Electrophilic fluorination at saturated carbon

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A Thesis Entitled

Electrophilic Fluorination at Saturated Carbon

Submitted by

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Memorandum

The work described in this thesis was carried out in the University of Durham between the 1st October 1997 and 30th September 2000. This thesis is the work of the author, except where acknowledged by reference, and has not been submitted for any other degree.

The work has been presented by the author, in part, at:

1. Electrophilic fluorination of hydrocarbon derivatives. R. D. Chambers, J. S. Moilliet, M. Parsons and G. Sandford. Presented at the 16th International Symposium on Fluorine Chemistry, University of Durham, Durham, July 2000.

2. Elemental fluorine for electrophilic fluorination. R. D. Chambers, M. Parsons and G. Sandford. I.C.I. Poster Session, University of Durham, Durham, December 1999

3. Elemental fluorine for electrophilic fluorination. R. D. Chambers, M. Parsons and G. Sandford. Graduate Seminar, University of Durham, Durham, June 2000.

And in paper or patent form in:

1. Electrophilic fluorination at saturated sites. R. D. Chambers, M. Parsons, G. Sandford and R. Bowden, *J. Chem. Soc., Chem. Commun.*, 2000, 959.

2. Elemental fluorine. Part 10. Selective fluorination of pyridine, quinoline and quinoxaline derivatives with fluorine-iodine mixtures. R. D. Chambers, M. Parsons, G. Sandford, C. J. Skinner, M. J. Atherton and J. S. Moilliet, *J. Chem. Soc., Perkin Trans. 1*, 1999, 803.

3. Selective nitrogen functionalisation of saturated C-H bonds. R. D. Chambers, M. Parsons and G. Sandford. UK Patent Application No 001093.4, 19 January 2000.

4. Fluorination of saturated hydrocarbons using elemental fluorine. R. D. Chambers, M. Parsons and G. Sandford. UK Patent Application No 9924705.8, 20 October 1999.

5. Fluorination of saturated hydrocarbons using N-F reagents (Selectfluor^{TM}). R. D. Chambers, M. Parsons and G. Sandford. UK Patent Application No. 9907214.2, 30 March 1999.

Nomenclature and Abbreviations

Throughout this work an 'F' in the centre of a ring denotes that all unmarked bonds on that ring are to fluorine.

The following abbreviations have also been employed:

NMR	Nuclear Magnetic Resonance
GC-MS	Gas Chromatography-Mass Spectrometry
IR	Infrared
DCM	Dichloromethane
TLC	Thin Layer Chromatography

Statement of Copyright

Abstract

Electrophilic Fluorination at Saturated Carbon

Mandy Parsons, University of Durham, 2000

Chapter 1 - Chapter 1 contains a discussion of the preparation and properties of elemental fluorine. A review of the use of elemental fluorine as a selective fluorinating in organic chemistry is given and the preparation and use of other selective fluorinating agents is also described.

Chapter 2 - Direct fluorination methodology for the preparation of selectively fluorinated hydrocarbon compounds was developed and used to prepare a range of both cyclic and acyclic fluoroalkanes.

Selectfluor^{TM}, a commercial fluorinating agent of the N-F class, was also used to prepare selectively fluorinated hydrocarbon compounds and the results of these experiments were used to gain information about the mechanism of the corresponding direct fluorination reactions. It was concluded that the direct fluorination reactions proceed via an aliphatic electrophilic substitution mechanism.

Chapter 3 - An amidation procedure which involves the use of elemental fluorine, boron trifluoride and acetonitrile was developed and used to prepare various selectively amidated hydrocarbon derivatives.

Chapter 4 - The selective direct fluorination of alkyl chains which are attached to an electron withdrawing group (EWG) was investigated to establish the effect that the EWG has on the fluorination reaction. For comparison, substrates were also reacted with Selectfluor^{TM}.

Chapter 5 - Chapter 5 is concerned with the preparation of selectively fluorinated N-containing heteroaromatic compounds using fluorine-iodine mixtures.

Chapters 6-9 - Experimental details of the work discussed in Chapters 2-5.

Contents

Chapter 1: Introduction

1.1 Organofluorine chemistry

Natural organofluorine compounds are exceedingly rare and none are isolated for application on a large scale. This means that organofluorine chemistry is essentially a 'man-made' branch of organic chemistry and in order to study this subject it is necessary to develop methods for the introduction of fluorine atoms into organic compounds. At first sight, this may appear to be of only academic interest but it is now well established that organofluorine compounds often possess useful properties. Some selectively fluorinated molecules show valuable biological activity and enhanced lipophilicity relative to their non-fluorinated counterparts while highly fluorinated compounds have high thermal stabilities and are often resistant to oxidation.[1]

It is not surprising, therefore, that a vast array of organofluorine compounds are utilised in a range of applications and some well-established examples are shown (Table 1.1).[1]

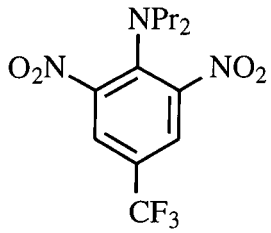
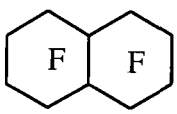
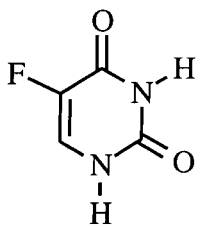
Compound	Application
CF_3CH_2F (HFC 134a)	Refrigerant, current replacement for CF_2Cl_2 (CFC 12)
 Trifluralin	Herbicide used in weed control
-$[CF_2]_n$- Polytetrafluoroethylene (PTFE)	Surface coating used on, for example, cooking utensils
 Perfluorodecalin	Inert fluid
 5-Fluorouracil	Anti-cancer agent

Table 1.1

Several reasons can be used to account for the large alterations which can be observed in the physical, chemical, and biological properties of a molecule when fluorine is included in the structure, which are:

- Fluorine has the highest electronegativity of all the elements (electronegativity = 4.0 on the Pauling Scale)[2].
- Fluorine forms the strongest single bond to carbon.[3]
- Fluorine has the second smallest Van Der Waals radius after hydrogen and can therefore replace hydrogen both singly and multiply in a molecule with minimum geometric disruption to the compound.
- Fluorine (when present as the -CF_3 group) can enhance the transport of aromatic compounds across biological membranes.

At present, the reagents and techniques which can be employed to prepare organofluorine compounds are limited and, therefore, it is necessary to develop further synthetic strategies which are convenient, economical, and safe.

A limited number of studies (Sections 1.2 and 1.5; pages 3 and 6 respectively) have demonstrated that elemental fluorine can be used to prepare organofluorine compounds and our group has been interested in promoting the use of elemental fluorine as a selective fluorinating agent for some time. Consequently, we have carried out a study which was aimed at developing procedures for the direct monofluorination of some organic compounds. The results of this study are outlined in Chapters 2-5 and this Chapter provides an introduction to these results. What follows therefore is an overview of the use of elemental fluorine in organic chemistry prior to World War II, an account of how fluorine is prepared, and some physical and chemical properties of elemental fluorine.

1.2 Historical development of direct fluorination

Elemental fluorine was first isolated by Henri Moissan[4] in 1886 upon electrolysis of anhydrous hydrogen fluoride in the presence of a little potassium fluoride. Consequently, Moissan was also the first chemist to react the halogen with organic materials and, in general, these 'reactions' proceeded vigorously and often resulted in combustion or detonation.

Following Moissan's attempts at direct fluorination, such reactions were not performed until around 1925 and, most likely, this was due to the expense of generating elemental fluorine and the fear of working with anhydrous hydrogen fluoride.

In 1926, Lebeau and Damiens[5] reacted elemental fluorine with wood charcoal and obtained carbon tetrafluoride. Unfortunately, the product was not characterised fully and the characterisation data which were offered were later found to be inaccurate. Ruff and Keim[6] also performed the fluorination of wood charcoal but, in contrast to Lebeau and Damiens, obtained pure carbon tetrafluoride from the reaction. This provided the first significant example of a solid phase fluorination reaction.

Bockmüller[7] pioneered the area of direct liquid phase fluorination and he was also the first to observe that direct fluorination reactions can show site selectivity. Only β– and γ-fluorobutyric acid were obtained when fluorine, diluted with carbon dioxide, was passed through a cooled solution of butyric acid and carbon tetrachloride.

A vapour phase fluorination technique was devised by Fredenhagen and Cadenbach[8] which consisted of mixing gaseous fluorine with organic vapours in meshes of copper. Bigelow and co-workers[9] developed this technique further and used it to demonstrate that a range of short chain hydrocarbon substrates can be converted to the corresponding perfluorinated compounds.

Further to the work by Ruff and Lebeau, Simons and Block[10] performed the solid phase fluorination of carbon and obtained a small range of short-chain fluorocarbon compounds from the reaction. Fluorination was carried out by exposing carbon to elemental fluorine in the presence of a catalytic amount of mercury.

It was soon realised that the fluorocarbon compounds prepared by Bigelow and Simons were extremely stable and resistant to uranium hexafluoride and this made them ideal materials for use in the Manhattan Project of World War II. The requirement of these and similar organofluorine compounds for the Manhattan Project generated great interest in fluorinated organic compounds and, consequently, organofluorine chemistry began to develop.

Following the Manhattan Project, Bigelow[11] developed a jet perfluorination system which can be used to fluorinate short-chain organic material. Later, chemists such as Lagow and Adcock made major advances towards understanding the reaction between elemental fluorine and various organic compounds and details of this work and other, more recent, direct fluorination reactions will be outlined in Sections 1.5 (page 6) and 1.6 (page 35).

1.3 Preparation of elemental fluorine

1.3.1 Electrochemical generation of elemental fluorine

Elemental fluorine is indirectly obtained from fluorspar (CaF_2) which is one of the principal fluoride-containing ores. Refined fluorspar is heated with sulfuric acid and the resulting mixture is distilled to give high purity anhydrous hydrogen fluoride. Hydrogen fluoride is then combined with potassium fluoride and the mixture is electrolysed to give elemental fluorine at the anode of the cell. Industrial cells use an electrolytic mixture which comprises of a 2:1 molar ratio of HF and KF and electrolysis is conducted at around 100°C using carbon anodes. These conditions are termed 'medium temperature' and are considered to be the most convenient for fluorine generation.

Cell corrosion presents a serious problem but can be reduced by constructing the cell from metals, such as copper, nickel, iron, and their alloys, which form protective metal fluoride surface coatings.

Rigorous details of the generation of fluorine can be found in a publication by Ellis and May.[12]

1.3.2 Chemical synthesis of elemental fluorine

The first and only chemical synthesis of elemental fluorine which is high yielding was reported by Christe[13]. (Scheme 1.1)

$$K_2MnF_6 + 2SbF_5 \xrightarrow{150°C} 2KSbF_6 + MnF_3 + 1/2F_2$$

Scheme 1.1

The synthesis is based on two fundamental facts, which are:

1) High-oxidation state transition metal fluorides which are thermodynamically unstable can be stabilised by anion formation. (Scheme 1.2)

$$MnF_3 + 1/2\,F_2 \longleftarrow \underset{\text{unstable}}{MnF_4} \longrightarrow \underset{\text{stable}}{MnF_6^{2-}}$$

Scheme 1.2

2) Weaker Lewis acids are displaced from their salts by stronger Lewis acids.

1.3.3 Preparation of elemental fluorine from uranium hexafluoride

It has been proposed that elemental fluorine can be obtained by creating an ionised plasma from uranium hexafluoride.[14] Uranium hexafluoride is a major by-product of the nuclear power industry and, due to its high volatility and corrosive properties, it is difficult to store. Any means to re-cycle fluorine from uranium hexafluoride is advantageous to the environment.

1.4 Physical properties of elemental fluorine

At room temperature, elemental fluorine exists as a pale yellow-green diatomic gas. Only one isotope (^{19}F) of fluorine occurs in nature but ^{18}F is known (half-life =109.8 min) and can be used as a radio-tracer[15]. Table 1.2[16] shows some physical properties of elemental fluorine and, for comparison, the corresponding values for the other non-radioactive halogens have also been included.

Property	F	Cl	Br	I
Atomic number	9	17	35	53
Melting point of X_2 (°C)	-216.8	-101.0	-7.25	113.6
Boiling point of X_2 (°C)	-188.1	-34.0	59.5	185.2
Ionisation energy of $X^{\bullet}$ (kJ/mol)	1680.6	1255.7	1142.7	1008.7
Electron affinity of $X^{\bullet}$ (kJ/mol)	332.6	348.5	324.7	295.5
Bond dissociation energy of X_2 (kJ/mol)	158.8	242.6	192.8	151.1
Distance X-X in X_2 (pm)	143	199	228	266

Table 1.2

1.5 Chemical properties of elemental fluorine

1.5.1 Reactivity of elemental fluorine

Fluorine is the most reactive of all the elements and, under appropriate conditions, forms compounds with all elements except the lighter noble gases, helium, neon, and argon. A number of metals form protective layers of metal fluoride when exposed to fluorine and this is often carried out deliberately to protect apparatus which is used to handle fluorine gas.

The reactivity of elemental fluorine is mainly due to two facts which are:

1) The F-F bond is very weak.

2) Fluorine forms very strong bonds with many other elements and some bond strengths are given (Table 1.3)[17].

Bond type	Bond Strength (kJ/mol)
F-F	**159**
C-F	**485**
H-F	**565**
Si-F	**565**

Table 1.3

1.5.2 Radical fluorination reactions

Under radical conditions, direct fluorination of organic compounds proceeds via a chain reaction.[18,19] Table 1.4 shows the mechanism and thermodynamic data of the

fluorination of a typical saturated hydrocarbon compound. For comparison, thermodynamic data for the corresponding chlorination reaction have also been included and, enthalpy changes are based on the use of methane carbon-hydrogen and carbon-halogen bond strengths at 298 K.[3]

Step	Reaction	X=F ΔH (kJ/mol)	X=Cl ΔH (kJ/mol)
Initiation			
1	$X_2 \longrightarrow 2X^{\bullet}$	159	243
Propagation			
2	$RH + X^{\bullet} \longrightarrow R^{\bullet} + HX$	-131	+8
3	$R^{\bullet} + X_2 \longrightarrow RX + X^{\bullet}$	-314	-107
Termination			
4	$R^{\bullet} + X^{\bullet} \longrightarrow RX$	-472	-349
5	$R^{\bullet} + R^{\bullet} \longrightarrow R\text{-}R$	-351	-351
Overall reaction	$RH + X_2 \longrightarrow RX + HX$	-445	-99

Table 1.4

Table 1.4 shows that each propagation step of the fluorination reaction is highly exothermic and, therefore, if this heat is not dissipated carbon-carbon bond scission is inevitable.

At room temperature the fluorine molecule is little dissociated (Scheme 1.3) and fluorine atoms are present in a concentration which is too low to initiate a radical chain reaction. However, a number of such reactions proceed vigorously at room temperature and this led Miller[20-22] to propose an alternative initiation process (Scheme 1.4).

$$F_2 \rightleftharpoons 2F^{\bullet}$$

$K = 2.1 \times 10^{-22}$ Pa

Scheme 1.3

$$RH + X_2 \longrightarrow R^{\bullet} + X^{\bullet} + HX$$

X=F; ΔH = +28 kJ/mol
X=Cl; ΔH = +249 kJ/mol

Scheme 1.4

Chlorine is also little dissociated at room temperature but it is unlikely that radical chain chlorination is initiated by the step shown in Scheme 1.4 (X=Cl) as this

step is very endothermic. Such reactions are usually initiated using light or thermal energy.

1.5.3 Selectivity of fluorination reactions

Anson and Tedder[23] established selectivity data for both fluorine and chlorine atoms using *n*-butane and *iso*butane as the substrates. The rate of substitution of hydrogen by halogen followed the expected pattern, which is: tertiary C-H > secondary C-H > primary C-H but fluorine atoms were found to be less selective than chlorine atoms and both types of reaction can be considered as unselective. (Table 1.5)

Type of Radical	**Relative Rate of Substitution***		
	Primary C-H	Secondary C-H	Tertiary C-H
Fluorine	1	1.3	2.5
Chlorine	1	4.6	10.3

*Reaction conditions: -81°C, liquid phase, no solvent, 20% F_2 or Cl_2 in N_2.

Table 1.5

This and other studies[24] show that fluorine atoms are extremely reactive and it is difficult to envisage the application of radical chain fluorination for the synthesis of selectively fluorinated organic compounds.

1.5.4 Perfluorination of organic compounds using elemental fluorine

Perfluorination of an organic compound involves the successive replacement of hydrogen by fluorine atoms and can be accomplished using elemental fluorine. Further fluorination of the intermediate fluorohydrocarbons by electrophilic fluorine atoms becomes progressively more difficult because the fluorine substitent(s) decrease the electron density of the substrate relative to the hydrocarbon starting material. Consequently, it may be necessary to increase the concentration of fluorine atoms towards the end of the process in order to achieve exhaustive fluorination. This can be accomplished by, for example, irradiating the process with UV light or adding an organic compound, such as benzene, which will react rapidly with elemental fluorine to give fluorine atoms.

As stated previously, this Thesis is primarily concerned with selective direct fluorination and, therefore, a full review of methodology which is used to achieve

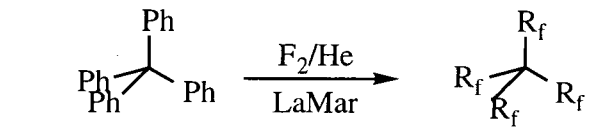
perfluorination is not appropriate. Consequently, what follows is a brief description of the most commonly used perfluorination techniques and for further information on this subject the reader is directed to more detailed articles.[19,24-27]

1.5.4.1 LaMar process

The LaMar perfluorination apparatus consists of a nickel tube which is packed with fine copper filings and is divided into several compartments. Each compartment is maintained at a different temperature so as to create a temperature gradient along the apparatus. The sample to be fluorinated is placed into the first compartment and fluorine, which is diluted with nitrogen or helium, is added. The substrate becomes progressively fluorinated and volatile and, therefore, it moves from the low temperature end towards the high temperature end of the reactor. Also, as reaction time increases, the concentration of fluorine used is also increased.

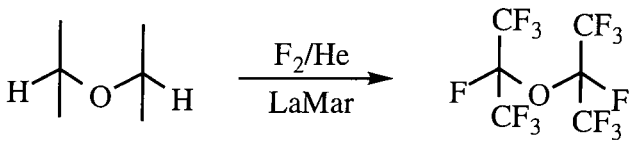
The copper packing in the reactor creates a large surface area of substrate and helps to dissipate the heat produced in the fluorination reaction.

The LaMar process is a batch process and relatively long reaction times are required to prepare perfluorinated compounds but it has been used to perfluorinate a wide range of substrates. A review of substrates which have been perfluorinated using the LaMar technique can be found in a recent review[24] and some representative examples are shown in Scheme 1.5[28,29].



96% yield

R_f=C_6F_{11}



49% yield

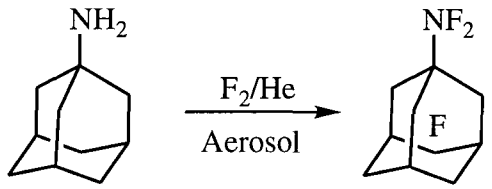
Scheme 1.5

1.5.4.2 Aerosol Perfluorination

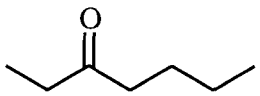
Aerosol fluorination is performed by adsorbing the organic substrate onto the surface of microscopic sodium fluoride particles and then allowing these particles to pass through the reactor as an aerosol spray. The reactor consists of a porous Monel® tube which is maintained so as to have a gradually increasing temperature along its length. The fluoride particles travel from the low to the high temperature end of the reactor and are gradually exposed to higher concentrations of fluorine gas. A UV source is attached to the reactor and is used to irradiated the reaction mixture at the final stage of the process to ensure perfluorination is achieved.

The sodium fluoride in the Aerosol process provides a heat sink, facilitates a large substrate surface area, and adsorbs some of the hydrogen fluoride produced in the fluorination reaction. The latter function acts to minimise acid-induced rearrangement and dehydrofluorination processes by the substrates.

Aerosol fluorination is a continuous process and has been used to prepare a large range of perfluorinated compounds[24] and some examples are shown. (Scheme 1.6)[30]



6% yield



perfluoroheptan-3-one

59% yield

Scheme 1.6

1.5.4.3 Exfluor Liquid Phase Fluorination

Exfluor fluorination involves the slow addition of both the substrate and elemental fluorine into a large excess of an inert solvent, such as 1,1,2-trichlorotrifluoroethane. To dissipate the heat produced in the fluorination reaction the mixture is stirred vigorously and if required, fluorine can be diluted with nitrogen and the substrate can be diluted with the reaction solvent. A hydrogen fluoride scavenger, such as sodium fluoride, is often added to the reaction mixture.

It has been claimed that exhaustive fluorination can be accomplished by the addition of a hydrocarbon compound, such as benzene, which reacts rapidly with elemental fluorine to give a high concentration of fluorine atoms.

1.5.4.4 Liquid Phase Photofluorination

Liquid Phase Photofluorination is performed by slowly adding the organic substrate into a perfluorocarbon which is saturated with neat fluorine. The reaction mixture is stirred vigorously, irradiated with UV light, and fluorine is added continually to the reaction mixture via the bottom of the reactor. Reaction conditions ensure that the substrate is present in a very low concentration relative to the fluorine. Only compounds which are partly fluorinated are suitable substrates for this perfluorination technique.

1.5.5 Other methods for perfluorination

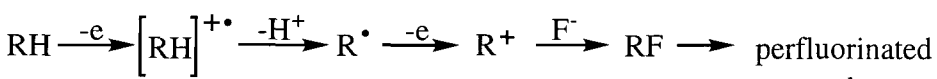
1.5.5.1 Electrochemical fluorination

Electrochemical fluorination (ECF) was devised during the Manhattan Project of World War II. It is performed by dissolving the organic substrate in anhydrous hydrogen fluoride (aHF) and then electrolysing the resulting solution to give fluorinated products at the anode and hydrogen at the cathode. Anodes are constructed from nickel and several studies[31] have shown that a nickel fluoride film forms on the anode surface and, that this film is required for fluorination to occur. Perfluorinated products are not soluble in hydrogen fluoride and so can be separated easily.

A wide range of substrates, such as ethers, amines, and sulphonyl- and carbonyl-containing compounds, can be fluorinated using ECF and, in general, the efficiency of the fluorination reaction is determined by the solubility of the substrate in aHF. The main advantage of this process is that many functional groups, such as those mentioned above, are retained in the fluorination reaction.

The mechanism of ECF is not understood and both carbocation and radical mechanisms have been advanced.

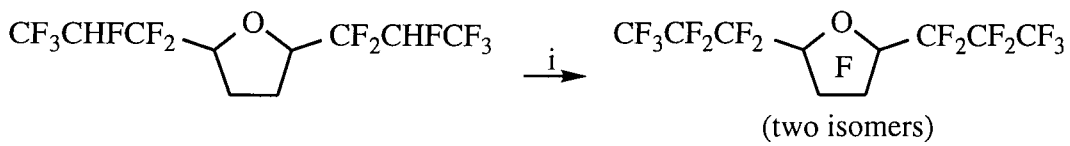
The carbocation mechanism involves oxidation of the organic substrate to give either a carbocation[32] or a radical-cation[33,34] -which then undergoes further chemical and electrochemical transformation to give a carbocation- (Scheme 1.7). The carbocation intermediate is attacked by fluoride ion and the whole sequence is repeated until perfluorination is achieved. It is difficult to envisage that ECF proceeds via this type of mechanism given that the oxidation potential of the substrate increases dramatically as the fluorine content of the substrate is increased.



Scheme 1.7

It has been proposed that an inorganic fluorinating agent, which is located on or in the surface of the anode, fluorinates the substrate. The actual fluorinating species may be fluorine atoms which are loosely bound to the anode surface, elemental fluorine, or a high valency nickel fluoride. It has been suggested[31] that the organic substrate is adsorbed onto the nickel fluoride surface and then fluorinated via a radical mechanism. Some experimental observations which support this postulation are as follows:

- As stated previously, the nickel fluoride film on the anode surface is crucial to fluorination.[31]
- Placing N,N-dimethyltrifluoromethane sulphonamide in an ECF cell which had a pre-formed anode surface and no current supply gave per- and partially fluorinated products which are identical to the products given by standard ECF.[35]
- Fluorination of some substrates, such as polyfluorinated alkene derivatives, using both ECF and elemental fluorine gives very similar products.[36]
- The replacement of hydrogen by fluorine in a range of partially fluorinated compounds was achieved using nickel fluorides, such as $RNiF_3$, NiF_4, and K_2NiF_6. Reactions were performed in anhydrous hydrogen fluoride at or below 20°C and an example is shown in Scheme 1.8.[37]



(two isomers)

i = $RNiF_3$, aHF (initiated at -28<T<-20°C for 2.5 h), 24 h.

Scheme 1.8

This study provides evidence for loosely bound fluorine atoms on the surface of the nickel anode.

1.5.5.2 Cobalt trifluoride

Cobalt trifluoride fluorination was also developed during the Manhattan Project and it can be carried out as either a batch or a continuous process.

Batch process - The organic substrate is vaporised and then passed over the fluorinating agent which is contained within a tubular reactor. The fluorination process is agitated continually and maintained at *ca.* 350°C. Spent fluorinating agent is regenerated in a separate stage using elemental fluorine.

For a given substrate, the heat of fluorination with cobalt trifluoride is approximately half that of the direct fluorination reaction (Scheme 1.9) and, consequently, fluorination using cobalt trifluoride is less likely to cause skeletal fragmentation of the organic substrate.

$$R_3C\text{-}H + 2CoF_3 \longrightarrow R_3C\text{-}F + HF + 2CoF_2 \quad \Delta H = -234 \text{ kJ mol}^{-1}$$

$$R_3C\text{-}H + F_2 \longrightarrow R_3C\text{-}F + HF \quad \Delta H = -445 \text{ kJ mol}^{-1}$$

Scheme 1.9

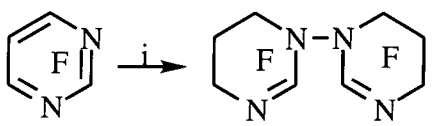
Continuous process - The cobalt trifluoride reactor has a bed which is mechanically-fluidised and elemental fluorine and the organic substrate can be added simultaneously to separate parts of the reactor. Most commercial cobalt trifluoride reactors use this method and many perfluorinated compounds including the Flutec® fluorocarbon compound range have been prepared using this process.

The mechanism of cobalt trifluoride fluorination has not been elucidated and remains under debate. Some authors[33] have claimed that reaction proceeds via a radical-cation mechanism (Scheme 1.10) but, as stated above, highly fluorinated compounds are not amenable to facile oxidation and it is difficult to rationalise the preparation of perfluorinated compounds using this mechanism.

$$RH \xrightarrow[CoF_3]{-e} [RH]^{+\bullet} \xrightarrow{CoF_3} [RHF]^{+} \xrightarrow{-H^+} RF \longrightarrow \text{perfluorinated product}$$

Scheme 1.10

Alternatively, reaction may proceed via a radical mechanism which involves the reaction of fluorine atoms with the substrate and, interestingly, tetrafluoropyrimdine (**1**) was converted to a polyfluorinated dimer (**2**) upon reaction with cobalt trifluoride (Scheme 1.11).[38] Observation of the dimeric species (**2**) is indicative of radical intermediates.



(**1**) (**2**)

20%, 74% Conv.

i = CoF_3, CaF_2, 175°C.

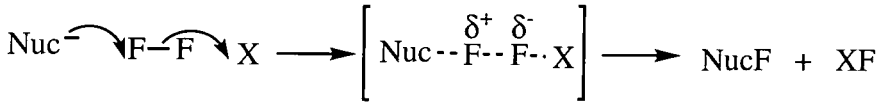
Scheme 1.11

1.5.6 Concluding remarks on radical fluorination

Radical fluorination reactions have been utilised for the preparation of a wide range of perfluorinated organic compounds and a number of techniques have been developed for this purpose.

1.5.7 Electrophilic fluorination using elemental fluorine

Fluorine atom reactions are highly unselective but selective direct fluorination is possible if elemental fluorine is promoted to act as an electrophile. It has been suggested that this can be achieved by the use of reaction media such as Lewis acids[39], protic acids[40,41], and solvents which have a high dielectric constant[40]. (Scheme 1.12)



X = Lewis acid, H^+, polar solvent.

Scheme 1.12

Reaction media of this type help stabilise the polar transition state and assist in heterolytic cleavage of the fluorine-fluorine bond by converting the developing fluoride ion into a good leaving group.

Other techniques which have been used to facilitate selective direct fluorination include:

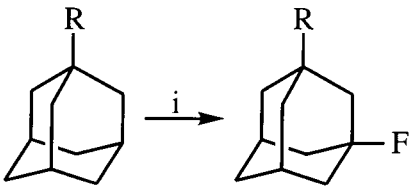
- The use of low reaction temperatures which minimise homolysis of the fluorine molecule.
- The use of reactor vessels and stirring procedures which facilitate good mixing of the reaction mixture and, therefore, minimise the formation of 'hot spots'.
- The use of elemental fluorine which has been diluted with an inert gas.

Selective direct fluorination has been reviewed at length prior to the start of 1997.[24,42-49]

This Thesis is concerned with selective direct fluorination and reports on this subject which appeared in the literature between January 1997 and May 2000 will be reviewed comprehensively in the following section. Chapters 2-5 detail the fluorination of both saturated sites and heteroaromatic compounds and, therefore, discussion of these topics has not been restricted to the 1997-2000 period.

1.5.7.1 Selective fluorination of sp^3 C-H bonds

Barton and co-workers[50-52] were the first to report that elemental fluorine can be used to prepare selectively fluorinated adamantane and steroid derivatives and some examples are shown in Scheme 1.13 and 1.14.

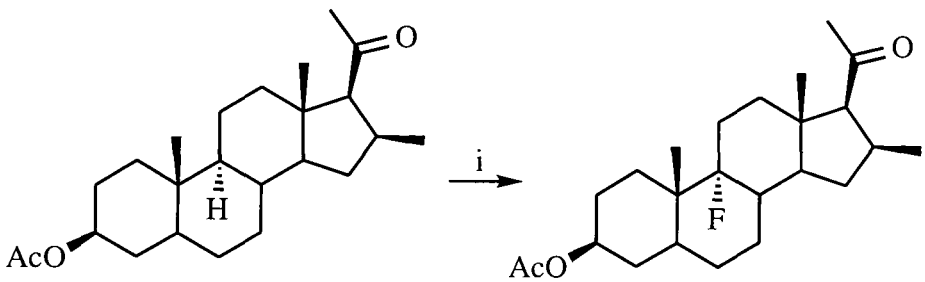


R=H; 84% yield

R=NHCOCF$_3$; 83% yield

i = 10-20% F_2/N_2, $CFCl_3$, -78°C.

Scheme 1.13



50% yield

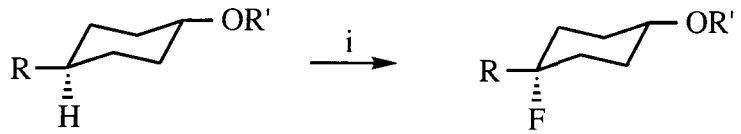
i = 10-20% F_2/N_2, $CFCl_3/CHCl_3$, -78°C.

Scheme 1.14

Product distributions are not altered by the addition of a known radical inhibitor and, consequently, Barton suggested that fluorination proceeds via an electrophilic fluorination mechanism.

Further to these studies, Rozen and co-workers[53-58] demonstrated that elemental fluorine can be used to selectively replace saturated C-H by C-F bonds in a range of organic molecules. The studies were limited to the replacement of tertiary sp^3 carbon-hydrogen bonds as they are, in general, more electron rich than secondary and primary carbon-hydrogen bonds.

Using 4-alkylcyclohexanol derivatives as substrates (Scheme 1.15) Rozen established that a polar reaction medium is essential for selective fluorination and, invariably, a 1:1 mixture of trichlorofluoromethane and chloroform was used as the reaction medium. When fluorination was attempted in less polar solvents, such as hydrocarbons or trichlorofluoromethane alone, only tars are detected.



R=Me, R'=$COC_6H_4NO_2$ *(p)*; 60% yield

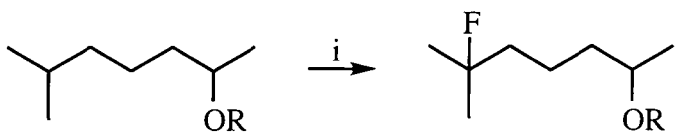
R=^{t}Bu, R'=$COC_6H_4NO_2$ *(p)*; 50% yield

i = 4% F_2/N_2, $CHCl_3/CFCl_3$, -70°C.

Scheme 1.15

In general, reactions were performed between -70 and -80°C and with fluorine which was diluted to less than 7% (v/v) in nitrogen.

It was found that the same factors which reduce the electron density of tertiary C-H bonds also reduce the rate of fluorination. For example, tertiary C-H bonds which are further from an electron withdrawing group are fluorinated preferentially to those which are closer. (Scheme 1.16)



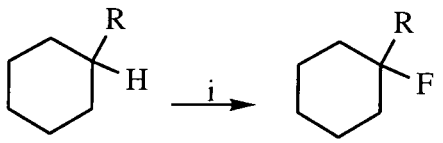
65% yield

R=$COC_6H_4NO_2$ *(p)*

i = 4-6% F_2/N_2, $CHCl_3/CFCl_3$, -70°C

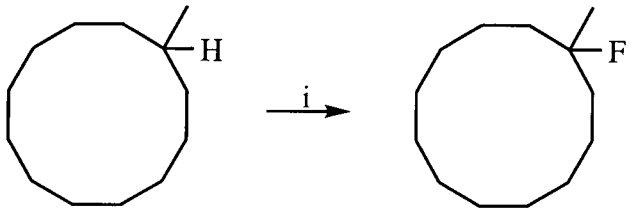
Scheme 1.16

Rozen also studied the fluorination of carbocyclic rings of various sizes and found that tertiary C-H bonds which are attached to three membered rings are not replaced but, instead, slow decomposition of the starting material results. The ease of ring fluorination increases as ring size is increased to approximately six carbon units. However, the selectivity of the fluorination of tertiary C-H bonds which are attached to rings which contain greater than six carbon atoms is poor. Rozen argued that this poor selectivity is due to the high ratio of primary and secondary carbon-hydrogen bonds relatively to tertiary. (Scheme 1.17)



60% yield

$R=(CH_2)_2COOCH_2CCl_3$

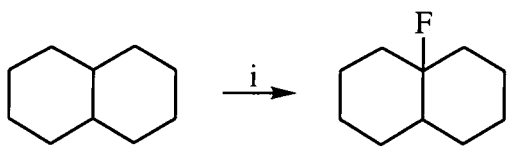


30% yield

i = 4-5% F_2/N_2, $CHCl_3/CHCl_3$, -75°C.

Scheme 1.17

The fluorination of straight chain, cyclic, and bicyclic compounds was addressed and retention of configuration was observed in all cases where the stereochemistry of the product was determined. (Scheme 1.15, 1.18, 1.19, 1.20)



trans - 80% yield

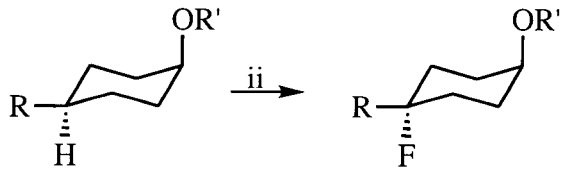
cis - 90% yield

trans ⟶ *trans*

cis ⟶ *cis*

i = 1% F_2/N_2, $CHCl_3/CFCl_3$, -75°C.

Scheme 1.18

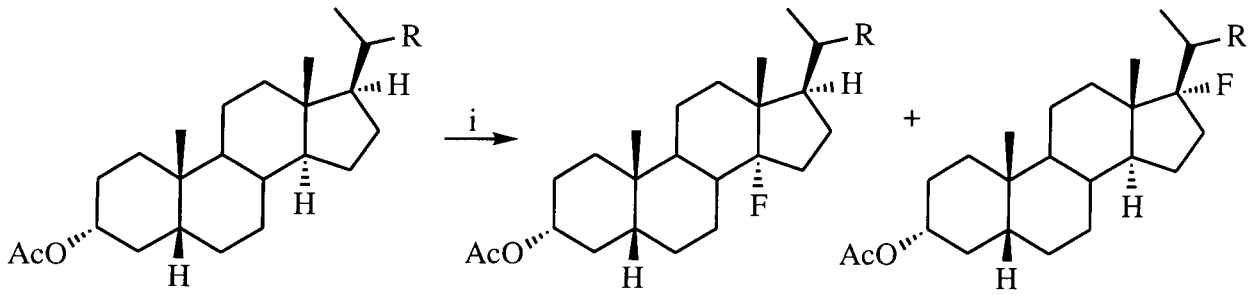


R=Me; 65%
R=^{t}Bu; 83%

R'=$COC_6H_4NO_2(p)$

ii = 4% F_2/N_2, $CHCl_3/CFCl_3$, -70°C.

Scheme 1.19

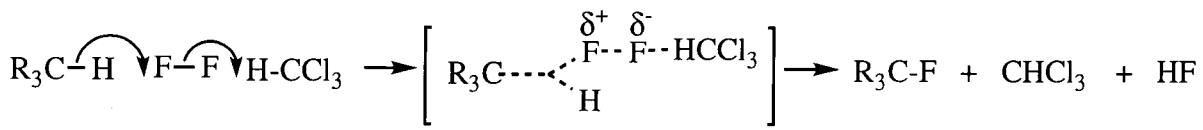


R=$CH_2CH_2CO_2CH_3$ 40% 15%

ii = 4-6% F_2/N_2, $CHCl_3/CFCl_3$, -78°C.

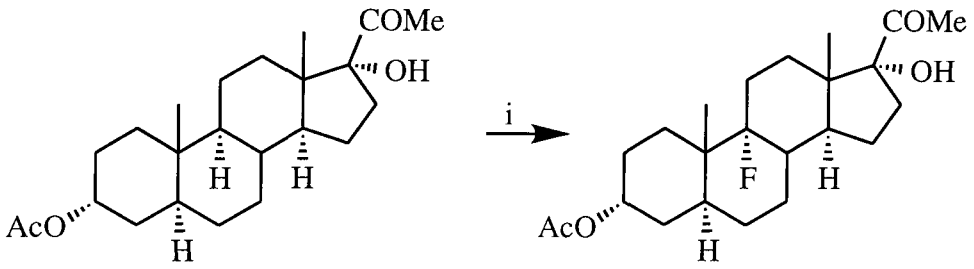
Scheme 1.20

In agreement with Barton, Rozen also proposed that the fluorination of saturated sp^3 C-H bonds proceeds via an aliphatic electrophilic substitution mechanism. It was argued that chloroform in the reaction medium assists nucleophilic attack on fluorine by acting as an acceptor for the developing fluoride ion. This results in formation of a three-centre two-electron transition state which collapses to give the fluorinated product and hydrogen fluoride. (Scheme 1.21)



Scheme 1.21

Rozen[59,60] prepared many selectively fluorinated steroids by placing electron withdrawing groups at strategic positions in the steroid structure and, as an example of this, 20-oxo-5α-pregnane-3α,17α-diol 3-acetate (**3**) was converted to a single monofluorinated product, 9-fluoro-20-oxo-5α-pregnane-3α,17α-diol 3-acetate (**4**), upon reaction with elemental fluorine. (Scheme 1.22).



(3) (4)

60% yield

i = 4-6% F_2/N_2, $CHCl_3/CFCl_3$, -75°C.

Scheme 1.22

Passing elemental fluorine through a mixture of cyclohexane and acetic acid gave fluorocyclohexane (18% yield) and other minor products.[61]

Recently, the fluorination of n-dodecane was performed in the presence of aluminium trifluoride.[62] Three types of aluminium fluoride were used in the investigation namely, α-AlF_3 (surface area =1 m^2/g), porous aluminium fluoride-a (PAF-a) (surface area = 30 m^2/g), and PAF-b (surface area = 75 m^2/g). Fluorination was performed by adsorbing n-dodecane onto the aluminium fluoride and then exposing the resulting mixture to neat fluorine. Some representative results are shown in Table 1.6.

Ratio of Fluorine: Substrate Used	**Solid Support**	**n-Dodecane Recovered (%)**	**CHF_2 (%)**	**CH_2F (%)**	**CHF (%)**
0.39	α-AlF_3	68.3	coke only		
0.37	PAF-a	81.2	4.1	18.1	77.8
0.48	PAF-b	79.2	2.2	28.5	69.3

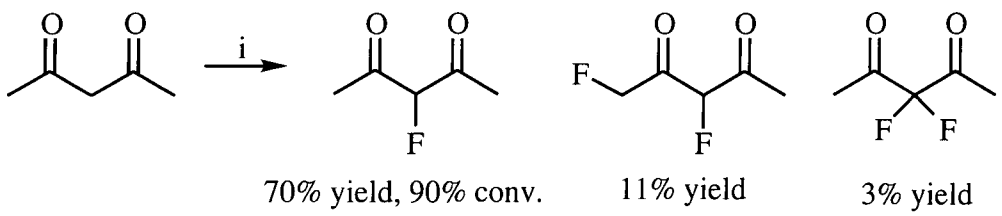
Table 1.6

It was observed that the selectivity of the fluorination reaction increases as the surface area of the aluminium fluoride support increases and it was suggested that the PAF protected most of the hydrocarbon chain from attack by elemental fluorine.

1.5.7.2 Carbonyl-containing compounds

Small fluorinated carbonyl-containing compounds can be used as building blocks for larger selectively fluorinated molecules and, therefore, the direct fluorination of simple carbonyl-containing compounds has been the focus of many studies.[24] In most cases, the carbonyl group was converted into the corresponding enol derivative, such as enol acetate or trimethylsilyl ether, prior to reaction with elemental fluorine. Such a transformation is necessary as, in general, keto-tautomers react with elemental fluorine to give a range of products, whereas, enol-tautomers give the corresponding α-fluorocarbonyl compound.

However, Chambers and co-workers found that the direct fluorination of various β-dicarbonyl compounds gives the corresponding α-fluorocarbonyl products without prior chemical conversion to an enol system.[63] (Scheme 1.23 shows an example.)

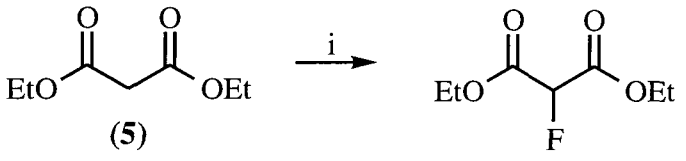


i = 10% F_2/N_2, HCO_2H, 10-15°C.

Scheme 1.23

The success of the fluorination reactions is attributed to the ability of the β-dicarbonyl compounds to enolise in the reaction solvent and, therefore, dicarbonyl compounds which have a high enol content and/or a high keto/enol rate constant in formic acid are fluorinated. Consequently, dialkylmalonates, which have a low enol content in formic acid, can not be selectively fluorinated using this methodology.

Following this study, the affect of metal salts on the direct fluorination of both β-dicarbonyl and various 2-substituted carbonyl compounds was studied.[64] It was found that hydrated copper(II) nitrate promotes the fluorination of diethyl malonate (**5**) to give a single monofluorinated product (**6**) in good yield. (Scheme 1.24) The selective fluorination of many other carbonyl compounds was catalysed using either copper or nickel salts and it is likely that these metal salts promote enolisation of the carbonyl-containing substrates.



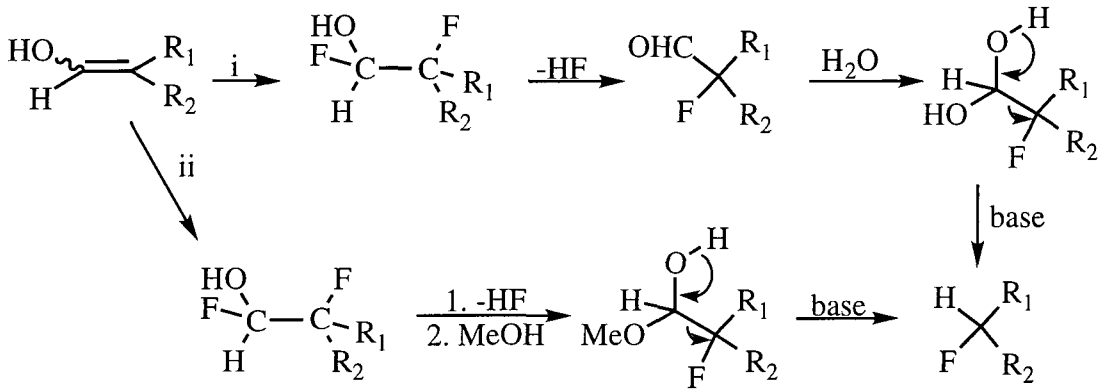
(5) (6)

78% yield, 100% conv.

i = 10% F_2/N_2, $Cu(NO_3)_2.2.5H_2O$ (10%), CH_3CN, ca. 5°C.

Scheme 1.24

Carbonyl-containing compounds which also contain an α-hydroxymethylene substituent, such as dimethyl hydroxymethylenemalonate, can be selectively fluorinated (Scheme 1.25) using elemental fluorine. Reaction proceeds via addition of fluorine to the carbon-carbon double bond followed by elimination of hydrogen fluoride. The resulting fluorinated products were then transformed to the corresponding α-fluorocarbonyl compounds.[65]



for example;

$R_1=R_2=CO_2Me$

$R_1=CO_2Et$, $R_2=COMe$

$R_1=CO_2Me$, $R_2=CN$

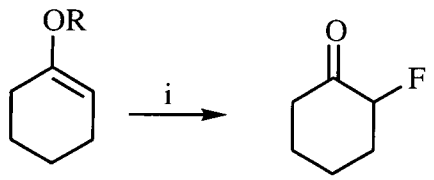
i = 3% F_2/N_2, CH_3CN or H_2O, -40 or 0°C.

ii = 3% F_2/N_2, CH_3CN/CH_3OH (29:1), -40 or 0°C.

Scheme 1.25

In this study, the hydroxymethylene substituent is employed as a directing and activating group and it can be removed easily after the fluorination reaction.

Various α-fluoroketones were prepared by treating simple ketone derivatives, such as enol acetates or trimethylsilyl ethers, with elemental fluorine in either acetonitrile or formic acid. For a given substrate, fluorination of the enol acetate gave a higher yield of the product.[66] (Scheme 1.26)



R=Ac, 56% yield, >95% conv.

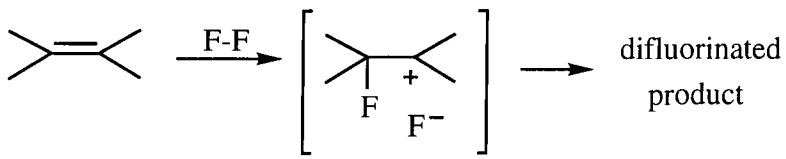
R=$SiMe_3$, 30% yield, 100% conv.

i = 10% F_2/N_2, CH_3CN, 0°C.

Scheme 1.26

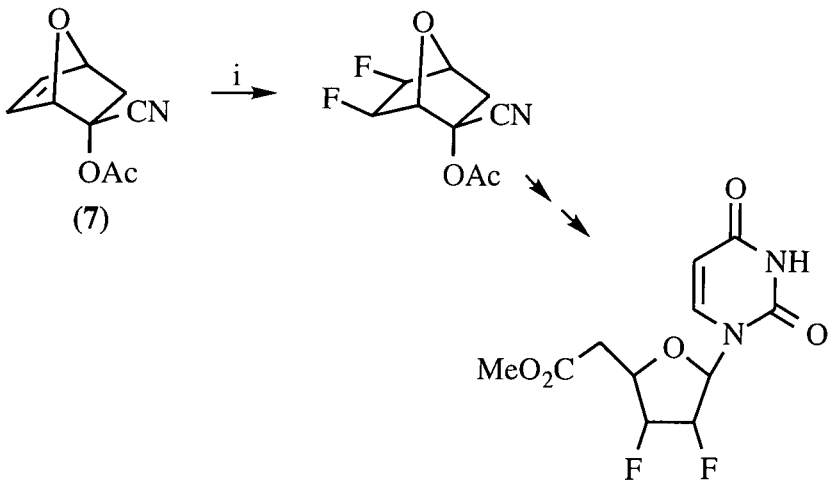
1.5.7.3 Carbon-carbon double bonds

Reaction of elemental fluorine with alkene compounds can result in preparation of the corresponding *syn*-1,2-difluorinated product.[24,42] It was suggested that the *syn* mode of addition results because the intermediate ion pair, which is bound tightly, collapses before carbon-carbon bond rotation can occur.[67] (Scheme 1.27)



Scheme 1.27

Recently, it has been shown that 2-cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl acetate (**7**) can be converted to the corresponding difluorinated product by passing elemental fluorine through a solution of **7** in $CFCl_3/CHCl_3$/EtOH (5 : 4 : 1). The major product from this reaction was then transformed to give a difluorinated ribofuranosyluracil (**8**).[68] (Scheme 1.28)



(7)

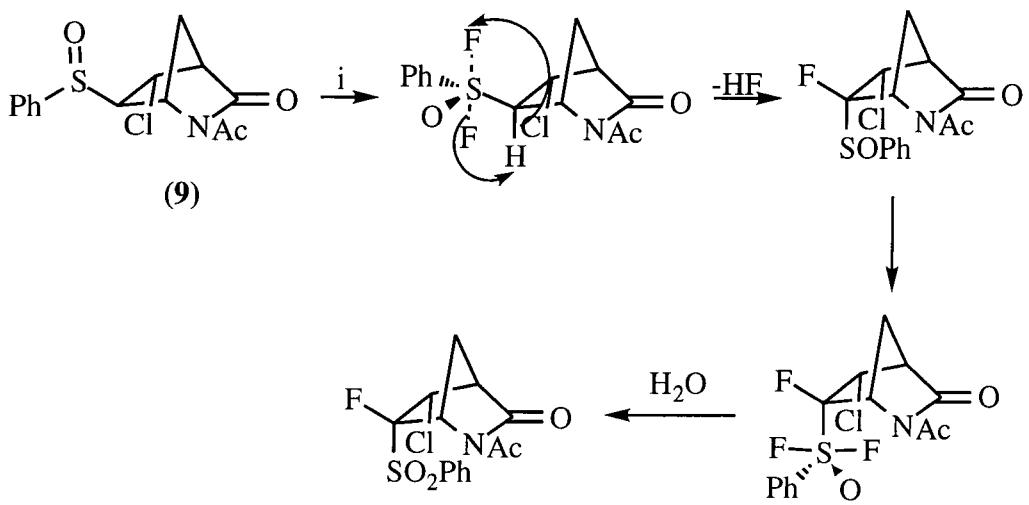
(8)

i = 5% F_2/N_2, $CFCl_3/CHCl_3$/EtOH, -78°C.

Scheme 1.28

1.5.7.4 Fluorination of sulfur containing compounds

Toyota and co-workers used elemental fluorine to prepare an S-fluoroazanorbornane derivative of **9** which undergoes spontaneous dehydrofluorination and stereoselective fluorine migration to give **10**.[69] (Scheme 1.29)



(9)

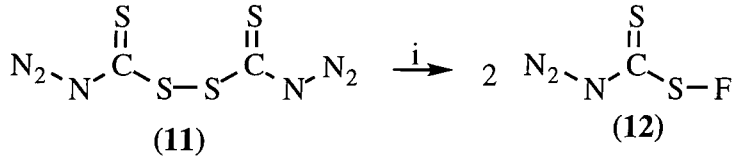
(10)

36% yield

i = 5% F_2/N_2, CH_3CN, -20°C.

Scheme 1.29

Azido-carbondisulfide (**11**) can be converted to fluoroazido-carbondisulfide (**12**) using an excess of elemental fluorine and this transformation exemplifies the use of elemental fluorine for the preparation of S-F containing compounds.[70] (Scheme 1.30)



(**11**) (**12**)

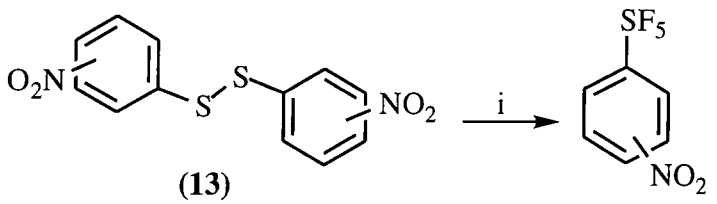
40% yield

i = neat F_2, SOClF, -100°C.

Scheme 1.30

Aromatic sulfurpentafluorides, such as (3- and 4-nitrophenyl)sulfurpentafluoride (**14, 16**) can be prepared by passing elemental fluorine through a solution which contains acetonitrile and the corresponding aromatic disufide.[71] (Scheme 1.31) Alternatively, both thiophenol and aromatic methyl thioether compounds can be used as starting materials.

However, substrates which contain a nitro group *ortho* to the sulfur group give, on reaction with fluorine, the corresponding sulfurtrifluoride derivative and it was reasoned that steric hindrance from the adjacent substituent prevents conversion of the trifluoride to the pentafluoride derivative.



(**13**) (**14 or 16**)

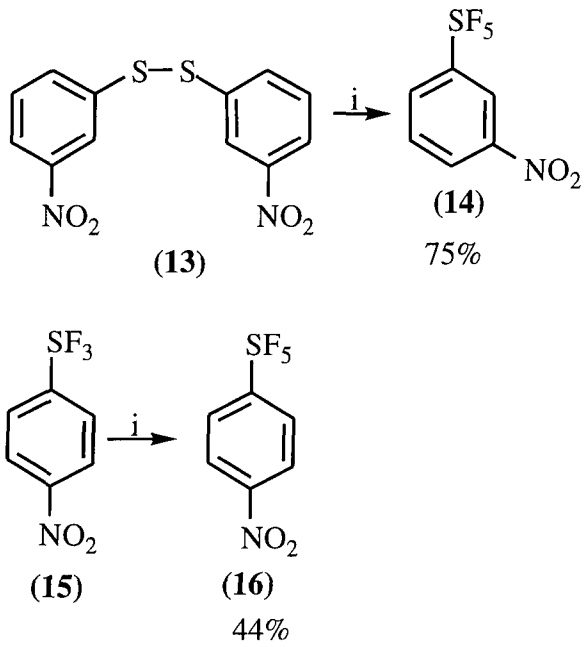
14 - 39% yield
16 - 41% yield

i = 10% F_2/N_2, CH_3CN, -5°C, 6-24 h.

Scheme 1.31

A microreactor system, which was designed specifically for direct fluorination, has been developed recently by Chambers and Spink[72] and fluorination of both di(*m*-nitrophenyl)disulfide (**13**) to (3-nitrophenyl)sulfurpentafluoride (**14**) and (4-nitrophenyl)sulfurtrifluoride (**15**) to the corresponding pentafluoride (**16**) was performed in this system. (Scheme 1.32) Reactions were carried out by dissolving the substrate in the reaction solvent and then injecting the resulting solution and

elemental fluorine into separate parts of the microreactor. However, (4-nitrophenyl)sulfurtrifluoride (**15**) was prepared from di(*p*-nitrophenyl)disulfide using a bulk fluorination process as the disulfide (**15**) is only sparingly soluble in the reaction solvent.



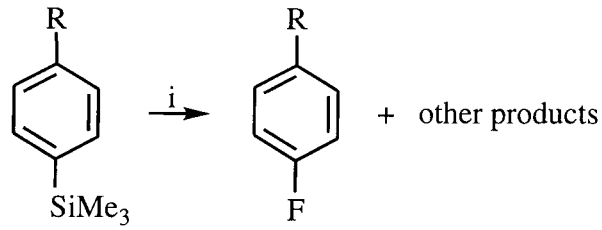
i = 10% F_2/N_2 (10 ml min^{-1}), CH_3CN (5 ml h^{-1}), room temp.

Scheme 1.32

1.5.7.5 Aromatic compounds

Selective direct fluorination of aromatic compounds has been the subject of a number of studies and, in general, product distributions are indicative of electrophilic aromatic substitution[24, 42].

In 1990, Chambers and Rock[73] investigated fluorodesilylation of arylsilanes using elemental fluorine (Scheme 1.33) as a general route to selectively fluorinated aromatic compounds and concluded that fluorination proceeds via an electrophilic process.

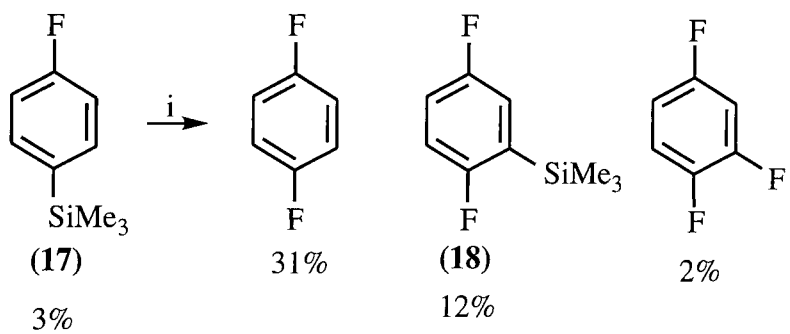


R=H; 16%
R=Cl; 16%
R=F; 26%

i = 10% F_2/N_2, CH_3CN, 0 or -30°C.

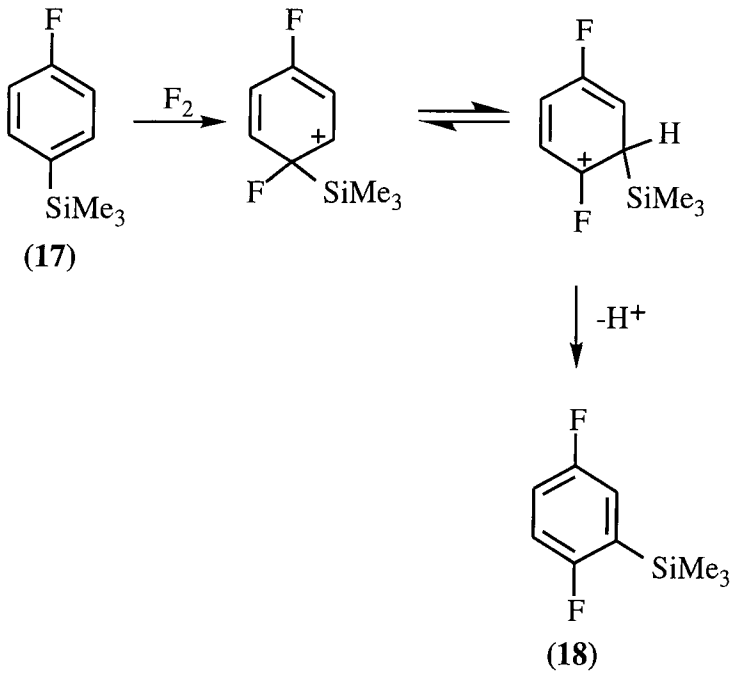
Scheme 1.33

Recently, Coe *et al.*[74] have also performed fluorodesilylation of an aromatic compound (4-fluorophenyltrimethylsilane (**17**)) by passing elemental fluorine, as a 10% mixture with nitrogen, through a mixture of the substrate and a solvent. (Scheme 1.34) Surprisingly, 2,5-difluorophenyltrimethylsilane (**18**) was also obtained and it was proposed that the by-product was produced via a 1,2-trimethylsilyl migration (Scheme 1.35).



i = 10% F_2/N_2, $CFCl_3$/MeOH (10%), -78°C.

Scheme 1.34



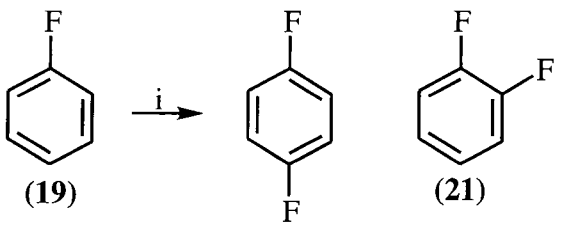
(17)

(18)

Scheme 1.35

Fluorodesilylation of fluorophenyltrimethylsilane (**17**) was attempted in a range of reaction media and it was found that both boron trifluoride and triflic acid catalyse the reaction. However, triflic acid was not pursued as a reaction solvent because it promotes proto-desilylation of the starting material.

Following the observation that triflic acid promotes selective direct fluorination, Coe *et al.*[41] investigated the affect of various acidic media on the direct fluorination of fluorobenzene (Scheme 1.36). Table 1.7 shows a sample of the results obtained from the investigation.



(19) (20) (21)

i = 10% F_2/N_2, low temp., solvent.

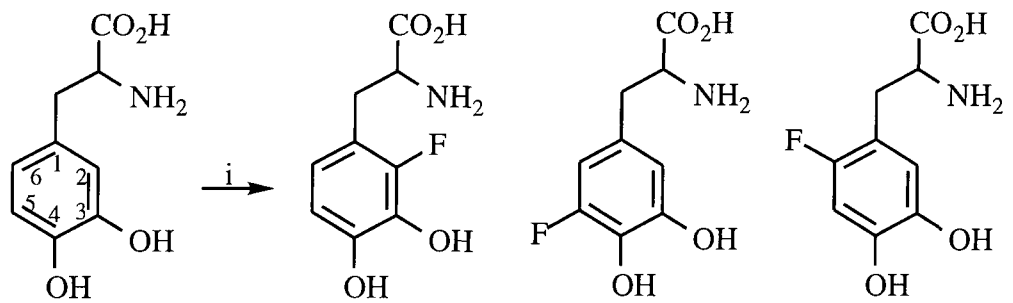
Scheme 1.36

Solvent System	S. M. Recovered (%)	Yield of 20 (%)	Yield of 21 (%)
$CFCl_3$-CF_3SO_3H (5%)	7	31	7
$CFCl_3$-CF_3SO_3H (5%) BF_3 (1.2 equiv.)	22	20	7
$CFCl_3$-CF_3CO_2H (10%)	16	8	3
CH_2Cl_2-CF_3CO_2H (50%)	67	2	0
CH_3CN-CF_3SO_3H (10%)	29	9	6

Table 1.7

Table 1.7 shows that $CFCl_3$-CF_3SO_3H (5%) promotes a fluorination reaction which is both more efficient and cleaner than all other reactions which were carried out. It is interesting to note that these results are consistent with the earlier observation by Chambers and co-workers[40] that some acidic media are excellent for promoting electrophilic fluorination.

Chirakal and co-workers[75] have also studied the affect that the reaction medium can have on the direct fluorination of an aromatic system (L-DOPA (**22**)). (Scheme 1.37)



(22)

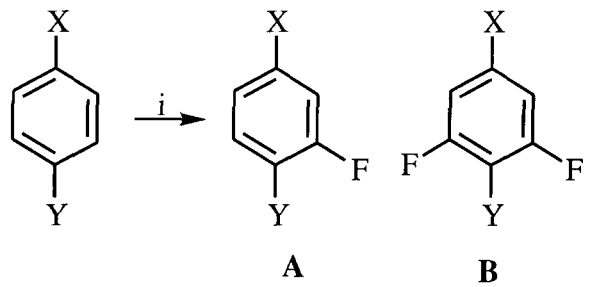
i = 1% F_2/N_2, acidic solvent, 4-10°C.

Scheme 1.37

Product distributions indicate that the site of fluorination can be influenced by the acidity of the reaction medium. For example, strong acids, such as tetrafluoroboric acid, encourage substitution of 6-H, whereas, weaker acids, such as formic acid, direct fluorination to the 2- and 5-positions of the starting material.

Reaction of elemental fluorine with a series of 1,4-disubstituted aromatic compounds was performed by Chambers and co-workers[76] to identify fluorobenzene

derivatives which may be prepared on an industrial scale using direct fluorination methodology. The fluorination of various nitrobenzenes, benzonitriles, phenols, and anisoles was carried out as shown (Scheme 1.38) and Table 1.8 shows a sample of the results.



A **B**

i = 10% F_2/N_2, HCO_2H, 10°C.

Scheme 1.38

X	Y	Conv. (%)	Yield of A (%)	Yield of B (%)
NO_2	OH	75	70	8
CN	NHAc	86	66	10
COOMe	OMe	92	51	9
Br	OH	90	22	4
NO_2	F	36	53	trace

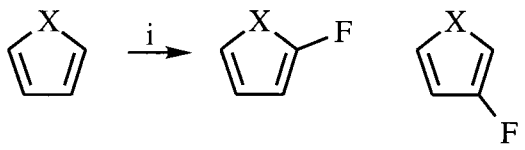
Table 1.8

In general, molecules which contain both an activating and deactivating group give good yields of fluorinated products and, as expected, the site of substitution is controlled by the substituent which is the most electron donating.

1.5.7.6 Heterocyclic and heteroaromatic compounds

1.5.7.6.1 Five membered rings

Fornarini and co-workers have prepared selectively fluorinated thiophene (**23**) and N-methylpyrrole (**24**) using elemental fluorine which was diluted with helium.[77,78] (Scheme 1.39)



X = S (**23**)	65%	35%
X = NMe (**24**)	20%	80%

i = 5% F_2/He, $CHCl_3$, -63°C, dark environment.

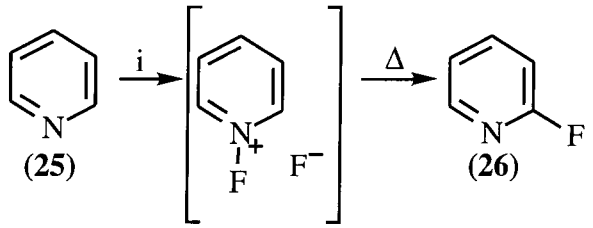
Scheme 1.39

To facilitate selective fluorination, low reaction temperatures and low fluorine concentrations were employed and, conversion values were kept between 5 and 10%.

Furan and pyrrole were also fluorinated but pyrrole gave only fluorinated tars and the main product from the furan reaction is a furan-fluorine addition adduct.

1.5.7.6.2 Six membered rings with one nitrogen atom

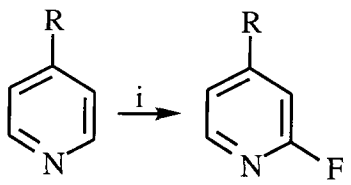
A small amount of 2-fluoropyridine (**26**) was obtained by Simons[79] upon reaction of elemental fluorine with pyridine (**25**). Meinert[80] also performed this reaction but obtained an N-fluoropyridinium fluoride which decomposed explosively at around 0°C to give a small amount of fluoropyridine (Scheme 1.40)



i = F_2, $CFCl_3$, -80°C.

Scheme 1.40

However, Van Der Puy[81] prepared various selectively fluorinated pyridine derivatives directly from the corresponding parent heterocyclic compounds using elemental fluorine. (Scheme 1.41)



R=Me, Et, ^{i}Pr, Ph, acetyl, CO_2Me

i = 10% F_2/N_2, $CF_2ClCFCl_2$, -25°C.

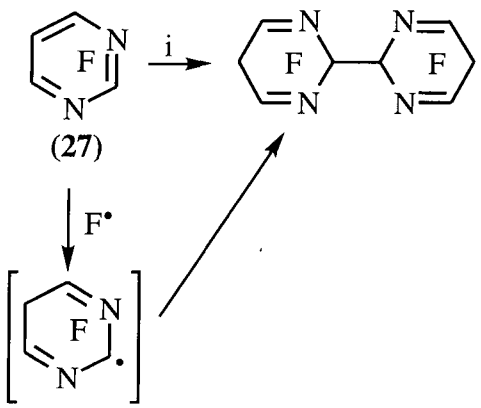
Scheme 1.41

It was proposed that fluorination proceeds via addition of elemental fluorine across the substrate carbon-nitrogen double bond.

Perfluoro-4-isopropylpyridine was found to be inert towards fluorination using elemental fluorine, as a 25% mixture with nitrogen, and a reaction temperature of -20°C.[82]

1.5.7.6.3 Six membered rings with two nitrogen atoms

Tetrafluoropyrimidine (**27**) was reacted with elemental fluorine as shown in Scheme 1.42 and it is interesting to note that fluorination was accompanied with dimerisation.[82]

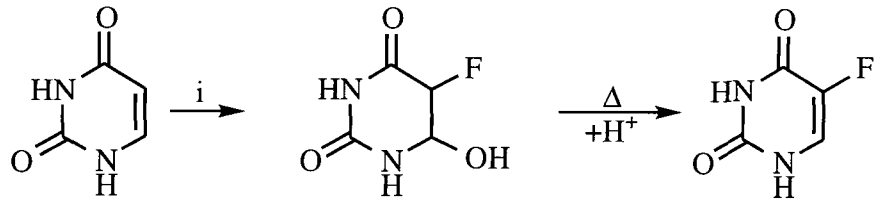


(**27**)

i = 30% F_2/N_2, $CF_2ClCFCl_2$, -20°C.

Scheme 1.42

5-Fluorouracil (5-FU) (**29**), an anti-cancer agent, is prepared on an industrial scale at a plant in Puerto Rico (SCM Corp.) by directly fluorinating uracil (**28**).[15] (Scheme 1.43)



(28) (29)

90% yield

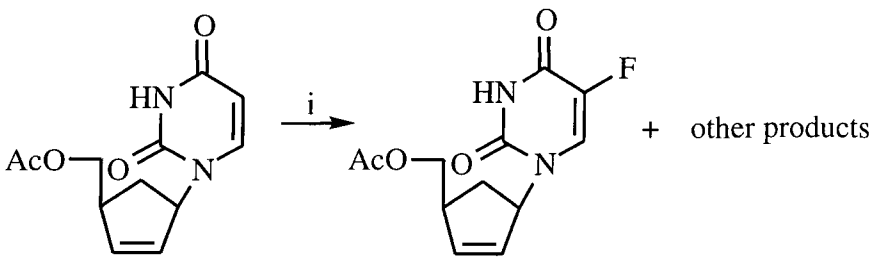
i = F_2/N_2, H_2O, 90°C.

Scheme 1.43

The direct fluorination of uracil (**28**) can also be performed in many other media[24, 42, 49] and, in all cases, reaction proceeds via addition adducts which either decompose (during the course of the reaction) to give 5-FU (**29**) or, can be promoted into doing so by the addition of a base or heat after the addition of fluorine.

The mechanism of fluorination of uracil (**28**) has been debated, Cech and co-workers[83] proposed that reaction (in acetic acid) proceeds via the addition of elemental fluorine across the carbon-carbon double bond of the substrate, whereas, Shiue *et al.*[84] suggested that reaction proceeds via formation of acetyl hypofluorite which then adds across the uracil double bond. In contrast to these processes, a radical-cation mechanism was suggested by Visser and co-workers[85].

Other pyrimidines and pyrimidine derivatives have also been directly fluorinated to give the corresponding fluorinated products.[49,86-88] For example, Coe *et al.*[87] reported the first example of the fluorination of a uracil nucleoside (Scheme 1.44).



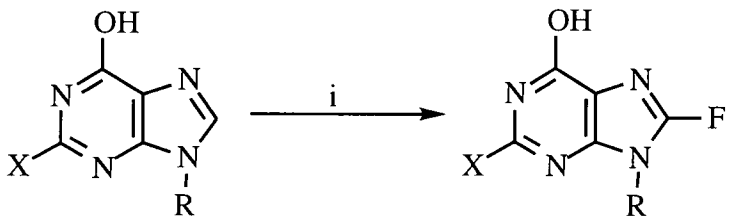
32% yield

i = 10% F_2/N_2, $CFCl_3$-$CHCl_3$-EtOH, molecular sieves, -78°C.

Scheme 1.44

1.5.7.6.4 Other heterocyclic nuclei

Various 8-fluoropurine derivatives can be prepared by reacting the corresponding purine with elemental fluorine[42,49,89]. (Scheme 1.45)[90]

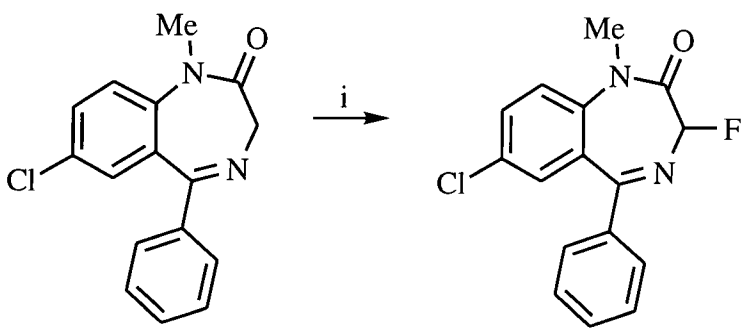


X=NH_2; R=(2-hydroxyethoxy)methyl; 10%
X=NHAc; R=(acetoxyethoxy)methyl; 30%

i = 1% F_2/He, EtOH, r.t.

Scheme 1.45

Reaction of fluorine with diazepam (**30**) gave 3-fluorodiazepam (**31**) in yields ranging from 24-63%. The yield of the product varies with both the substrate : fluorine ratio and the type of reaction medium employed. The use of reaction solvents which have low polarity results in higher product yields.[91] (Scheme 1.46)



(**30**) (**31**)

solvent = $CHCl_3$; yield =63%
solvent = MeCN; yield =21%

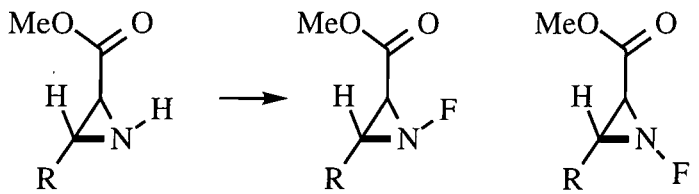
i = 0.5% F_2/Ne, $CHCl_3$ or MeCN, room temp.

Scheme 1.46

Details regarding the direct fluorination of other heterocyclic compounds can be found in reviews.[42, 24, 49]

1.5.7.6.5 Fluorination at nitrogen

Some N-fluorinated methoxycarbonylaziridine compounds (**32A, B**) were prepared by passing fluorine through a solution of the aziridine in 1,1,2-trichlorotrifluoroethane and both starting materials (R=H and CF_3; Scheme 1.47) underwent smooth fluorination and gave, in each case, a single stereospecific product.[92]



R=H (**32A**), CF_3 (**32B**) 0 >70% yield

i =14% F_2/N_2, freon 113, NaF, -5°C.

Scheme 1.47

Many other N-fluorinated compounds have been prepared due to the fact that some act as electrophilic fluorinating agents. The synthesis and application of such compounds will be described in Section 1.6.2 (page 36).

1.6 Electrophilic fluorinating agents

Elemental fluorine can be employed to prepare a range of selectively fluorinated organic compounds but the wide-spread use of this reagent has been limited due to its extreme toxicity and high reactivity.

In an attempt to develop methods for selective fluorination which avoid the use of elemental fluorine, much attention has been devoted to the preparation of electrophilic fluorinating agents which are suitable for general laboratory use. With a few exceptions, electrophilic fluorinating agents can be categorised as either O-F or N-F and both types have been reviewed extensively.[93, 94, 95]

In Chapter 2 of this Thesis the fluorination of some hydrocarbon compounds using various fluorinating agents is detailed and, therefore, a description of the preparation and application of such reagents is given in the following section.

1.6.1 O-F Reagents

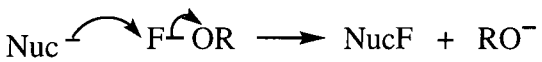
Some well-established O-F reagents are shown (Scheme 1.48)[94]. With the exception of CF_3OF, most O-F reagents are relatively unstable at room temperature and, consequently, must be prepared *in situ* and used without purification.

CF_3OF	$CsSO_4F$
Trifluoromethyl hypofluorite	Caesium fluoroxysulfate
CH_3CO_2F	R_fCO_2F
Acetyl hypofluorite	Perfluoroacyl hypofluorite

Scheme 1.48

O-F reagents are usually prepared by passing elemental fluorine through a suspension of either the potassium or sodium salt of the acid or alcohol to be O-fluorinated.

A representation of the fluorination of an organic substrate using an O-F reagent is shown (Scheme 1.49). The reagents are designed such that the oxygen atom is part of a good leaving group and, therefore, the reagent delivers electrophilic fluorine to a relatively nucleophilic substrate.



Scheme 1.49

Fluorination of substrates which are relatively electron rich, such as aromatic, carbanion, enolate and alkene compounds, can be achieved using OF regents.

1.6.2 N-F Reagents

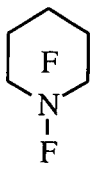
N-F fluorinating agents are relatively stable and were developed as alternatives to O-F reagents which are less convenient. A range of N-F reagents is available commercially and are suitable for general laboratory use.

Most N-F reagents are prepared using elemental fluorine although some are prepared using other fluorination methods, such as cobalt trifluoride and electrochemical fluorination.

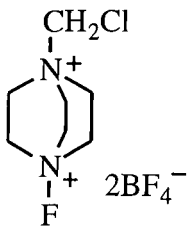
N-F reagents can be categorised as either neutral or ammonium quaternary salts and some representative examples are shown in Scheme 1.50[93].

$(PhSO_2)_2N\text{-}F$

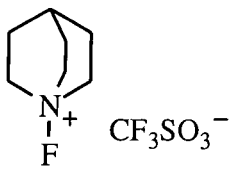
N-Fluorobenzenesulfonimide (NFSI)



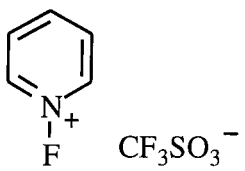
N-Fluoroperfluoropiperidine



N-Fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluorborate) (Selectfluor^{TM})



N-Fluoroquinuclidinium triflate



N-Fluoropyridinium triflate

Scheme 1.50

A range of compounds which include aromatics, enolates, carbanions, alkenes, organometallics and sulfides can be fluorinated using N-F fluorinating agents.

1.6.3 Other electrophilic fluorinating agents

Xenon difluoride can be made by direct combination of its constituent elements and the formation and utilisation of this fluorinating agent has been reviewed at length.[96]

Recently, a new class of fluorinating agents has been developed which is based on polyvalent selenium and tellurium.[97] $PhSeF_3$ **(33)**, $PhSeF_5$ **(34)** and $PhTeF_5$ **(35)** were all prepared using xenon difluoride (Scheme 1.51) and then used to fluorinate a small range of alkene compounds.

$$Ph_2Se_2 + 3XeF_2 \xrightarrow[-Xe]{DCM,\ r.t.} 2PhSeF_3 \quad (\mathbf{33})$$

$$Ph_2X_2 + 5XeF_2 \xrightarrow[-Xe]{DCM,\ r.t.} 2PhXF_5$$

X=Se (**34**), Te (**35**)

Scheme 1.51

Aromatic hypervalent iodine fluorides[98,99] and N_2F^+ and NF_4^+ salts [100,101], such as $N_2F^+AsF_6^-$, $NF_4^+AsF_6^-$, and $NF_4^+SbF_6^-$, have also been used as electrophilic fluorinating agents.

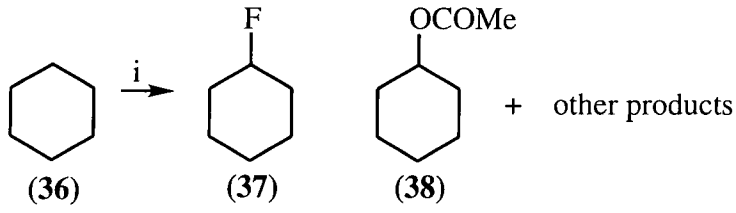
1.6.4 Selective fluorination of saturated C-H sites using electrophilic fluorinating agents

Studies which concern the selective fluorination of saturated C-H bonds using electrophilic fluorinating agents other than elemental fluorine are very rare and what follows is a review of such transformations which have been reported in the literature.

1.6.4.1 Trifluoromethyl hypofluorite and acetyl hypofluorite

Barton and co-workers[50] have prepared some monofluorinated adamantane[51] and steroid[51] derivatives using CF_3OF as the fluorinating agent and, in general, reactions were carried out at -25°C in the presence of a radical inhibitor.

The fluorination of cyclohexane (**36**) using trifluoromethyl hypofluorite[102] yielded fluorocyclohexane (**37**) (44%) as the major product, whereas, reaction of this hydrocarbon compound with acetyl hypofluorite[61] gave acetoxycyclohexane (**38**) (32%) predominantly and a small amount of fluorocyclohexane (**37**) (6%) (Scheme 1.52).



(36) (37) (38)

6% yield 32% yield

i = CH_3CO_2F, CH_3CO_2H.

Scheme 1.52

1.6.4.2 Oxygen difluoride

Oxygen difluoride reacts with various adamantane derivatives to give the corresponding 1-fluoroadamantane derivatives.[103]

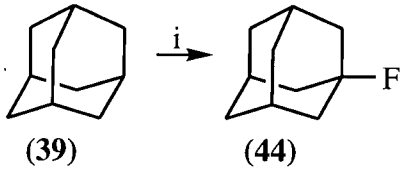
1.6.4.3 Caesium fluoroxysulfate

The selective fluorination of hydrocarbon compounds, such as cyclohexane (**36**), adamantane (**39**), cycloheptane (**40**), and norbornane (**41**) and can be achieved using caesium fluoroxysulfate.[104] (Scheme 1.53)

RH $\xrightarrow{i}$ RF

85% yield

RH=cyclohexane (**36**), cycloheptane (**40**), norbornane (**41**)
RF=fluorocyclohexane (**37**), fluorocycloheptane (**42**), 2-fluoronorbonane (**43**), respectively.



(39) (44) + 2-fluoro- and polyfluorinated adamantane

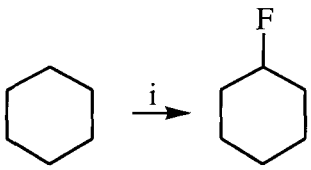
62% yield

i = $CsSO_4F$, CH_3CN, 35°C, 30 min.

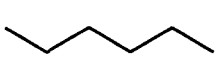
Scheme 1.53

1.6.4.4 Xenon difluoride

Zupan and Zajc[105] performed the fluorination of adamantane (**39**), hexane (**45**) and cyclohexane (**36**) by heating a deficiency of the hydrocarbon compound with xenon difluoride in a container which had a Teflon® surface. (Scheme 1.54)

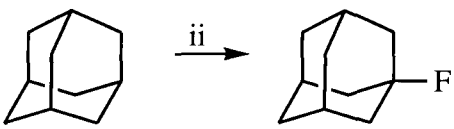


(**36**) (**37**)
18% yield



1-, 2- and 3-fluorohexane

(**45**) 28%, 42% and 30% yield respectively



(**39**) (**44**) + 2-fluoro- and polyfluorinated adamantane
60% yield

i = 0.2 XeF_2, 105°C, 2.5 h.
ii = XeF_2, 105°C, 70 min.

Scheme 1.54

Podkhalyuzin and Nazzrova[106] have also reported that adamantane (**39**) can be selectively fluorinated at the 1-position using xenon difluoride as the fluorinating agent but, in this study, carbon disulfide was used as the reaction solvent.

1.6.4.5 NF reagents

Fluorination of methane using N_2F^+ and NF_4^+ salts was reported to give a mixture of mono-, di-, and trifluoromethane but, if a very large excess of methane was employed, only fluoromethane was obtained.[100]

1.7 Conclusions

Organofluorine compounds are highly useful but do not occur in nature and, consequently, must be prepared in the laboratory. Elemental fluorine can be used to synthesise such compounds and, under radical reaction conditions, elemental fluorine can be utilised for the preparation of highly fluorinated compounds.

Selective direct fluorination can be achieved by encouraging elemental fluorine to act as an electrophile and many selectively fluorinated organic compounds have been prepared using direct fluorination methodology.

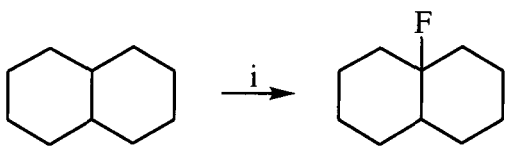
The wide-spread use of elemental fluorine has been limited due to its toxicity and reactivity and, therefore, electrophilic fluorinating agents have been developed as alternatives. These reagents are highly useful laboratory reagents but it is unlikely they will have any large scale industrial applications.

Chapter 2: Fluorination of Hydrocarbon Compounds

2.1 Introduction

Selective direct fluorination of hydrocarbon compounds is largely limited to the work of Rozen and co-workers[53-58] (Section 1.6.1; page 16) who performed the replacement of tertiary C-H by C-F bonds using a reaction medium of chloroform and trichlorofluoromethane (Scheme 2.1 shows a typical example). Such reactions can proceed with excellent regio- and stereoselectivity but the methodology exhibits a number of serious limitations which are:

- Substitution of only tertiary carbon-hydrogen bonds was attempted (is possible ?).
- Trichlorofluoromethane was used in the reaction medium and this solvent is now banned in accordance with the Montreal Protocol[107].
- Fluorination is carried out at very low reaction temperatures, which are not generally applicable on an industrial scale.
- Fluorine is used in a very dilute form (usually 1-5% in nitrogen).
- Relatively large volumes of reaction solvent are employed; a typical reaction mixture comprises 1 g of substrate and 400 cm^3 of solvent.



trans - 80% yield

cis - 90% yield

trans → *trans*

cis → *cis*

i = 1% F_2/N_2, $CHCl_3/CFCl_3$, -75°C.

Scheme 2.1

We were also interested in exploring the use of elemental fluorine for the preparation of selectively fluorinated hydrocarbon compounds and, consequently, the first part of this chapter outlines our approach to identify reaction conditions which can promote such a transformation. Following this, the scope of the conditions was investigated by attempting the selective fluorination of a range of hydrocarbon compounds.

Before the results of these studies are outlined, a description of the apparatus which was used to perform all direct fluorination reactions will be given. Further details on the use of elemental fluorine in the laboratory can be found in the experimental section (page 123).

2.2 Apparatus used to perform direct fluorination reactions

Fluorination reactions were carried out in a glass reactor which was fitted with an overhead stirrer and fluorine was supplied to the bottom of the reaction vessel using a PTFE dip-pipe. Exit gases were piped from the reactor to a scrubbing tower which was filled with soda lime.

The fluorination rig was constructed from stainless tubing and fittings and stainless steel or Monel® valves as shown in Figure 2.1.

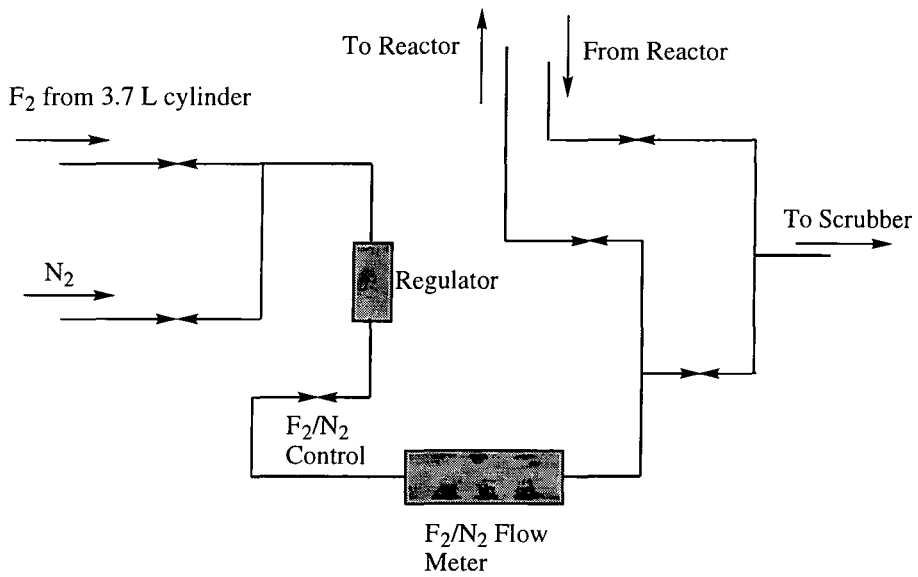


Figure 2.1

2.3 Solvent survey

Previous work[40] carried out by members of the Chambers group in Durham has shown that acid reaction media are excellent for promoting direct electrophilic fluorination of some aromatic compounds. This was established by performing the fluorination of a model compound, 4-fluorobenzoic acid, in a range of media.

We reasoned that acidic media may also promote the selective direct fluorination of hydrocarbon compounds and, therefore, a similar approach to the earlier study was adopted. For comparison, solvents which are non-acidic have also been employed.

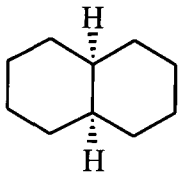
cis-Decalin (**46**) was selected as the model hydrocarbon compound because the selective fluorination of this substrate using elemental fluorine has been reported by Rozen and co-workers[108] and the product, *cis*-9-fluorodecalin, can be identified easily using ^{19}F NMR spectroscopy.

2.3.1 Preliminary solvent survey

Fluorination of *cis*-decalin (**46**) was performed by passing elemental fluorine, as a 10% mixture with nitrogen, through a cooled (0°C), stirred mixture or solution of decalin (**46**) and the reaction solvent. In a typical reaction, fluorine was passed at a rate of 10-15 mol hr^{-1} over approximately 16-18 hours and after addition of all the fluorine, the reaction mixture was poured into water and neutralised using aqueous sodium bicarbonate. Products were extracted using dichloromethane and vacuum transfer gave a colourless liquid and, in some cases, a brown solid (tar) remained in the distillation vessel. The amount of *cis*-9-fluorodecalin (**47**) which was present in the crude product was determined by adding a known amount of fluorobenzene to a known amount of crude product and then analysing the resulting mixture using ^{19}F NMR spectroscopy. The amount of starting material which remained after the reaction was calculated by relating the amount of fluorodecalin to the amount of decalin using the gas chromatograph of the crude product. GC response factors were taken into consideration when performing the latter calculation.

On occasion '% area' values have been given in the following text. These values correspond to the relative peak area of a given product in the gas chromatograph of the crude product mixture. It should be noted that response factors were not calculated for products which were not isolated and, therefore, '% area' values quoted for by-products should be taken as approximate.

The results from these analyses are shown in Scheme 2.2 and Table 2.1. The isolation of *cis*-9-fluorodecalin (**47**) is described in section 2.4.1 (page 50).



(46)

i - 4-5 equiv. 10% F_2/N_2, solvent, 0°C.

Scheme 2.2

Solvent	***cis*-9-Fluorodecalin (47) Yield[a] (Conv.) %**	**Tar %**
Acetonitrile fluorine : substrate = 1:1	<10 (13)[b]	0
Acetonitrile fluorine : substrate = 5:1	57 (64)	0
Acetonitrile fluorine : substrate = 16:1	10 (99)[b]	13
Propionitrile	50 (78)	0
Formic acid (decalin : fluorine = 1:1)	0 (2)[b]	trace
Sulfuric acid	0 (25)[b]	25
Trifluoroacetic acid	<1 (69)[b]	33
Trichlorotrifluoroethane[c]-triflic acid (1:1)	<1 (100)[b]	28
Trichlorotrifluoroethane[c]-triflic acid (19:1)	<1 (80)[b]	28
Boron trifluoride-DCM[d] (1:20)	0 (91)[b]	9
Boron trifluoride-DCM[d] (1:5)	0 (92)[b]	8
α,α,α-Trifluoroethanol	0 (61)[b]	0
Trichlorotrifluoroethane[c]	8 (85)	28
DCM[d] (decalin:fluorine = 1:5)	<1 (4)[b]	0
DCM[d] (decalin:fluorine = 1:10)	<1 (11)[b]	0
Nitromethane	33 (97)	24

Table 2.1

[a] - After work-up.
[b] - Conversion was estimated using GC-MS.
[c] -Freon 113.
[d] -Dichloromethane.

Description of Table 2.1 - The third column of Table 2.1 displays the amount of tar produced in each reaction and the value quoted corresponds to the weight percentage of tar relative to the amount of starting material which was used in the reaction.

In most reactions, products other than 9-fluorodecalin were produced and details of these by-products are given in the following text (full details can be found in the Experimental section of this chapter). It is very important to note that by-products were not isolated and, therefore, the identity of these compounds is based on mass spectral data only.

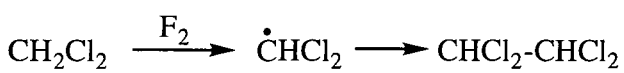
Acetonitrile - Fluorination of *cis*-decalin **(46)** using one molar equivalent of fluorine resulted in low conversion of starting material and a very clean reaction. In contrast, the use of a large excess (16 molar equivalents) of elemental fluorine gave a crude product mixture that contained a large number of products which could not be identified and a significant amount of tar.

Acetonitrile and propionitrile - Using five molar equivalents of elemental fluorine and a nitrile solvent gave a product mixture which contained *cis*-9-fluorodecalin **(47)** in good yield. Some by-products, such as difluorodecalin and an unsaturated decalin derivative, were observed but were present in small (<10 area %) or trace (< 1 area %) amounts.

Formic acid - Starting material (*ca.* 100%) was recovered from this reaction.

Sulfuric acid, trifluoroacetic acid and triflic acid - The crude products from all of these reactions contained a large amount of tar (>25%), a large amount of starting material and, with the exception of the sulfuric acid reaction, large amounts of unsaturated decalin derivatives.

Dichloromethane - Starting material (>89 area %), tetrachloroethane, and products which could not be identified were observed in the product mixtures from these reactions. Tetrachloroethane may have formed as shown in Scheme 2.3.



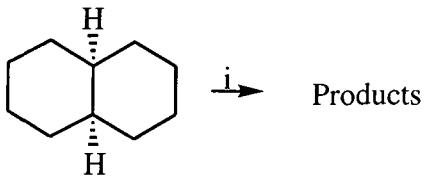
Scheme 2.3

1,1,2-Trichlorotrifluoroethane (Freon 113) - Direct fluorination of *cis*-decalin **(46)** in trichlorotrifluoroethane gave mono-, di-, tri-, and tetrafluorodecalin and unsaturated decalin derivatives and all of these products were present in a small amount (<10%). Many products which could not be identified and tar (28%) were also detected.

α,α,α-Trifluoroethanol - The product mixture from this reaction contained many unidentified products (<10%), unsaturated decalin derivatives (<10%), and starting material.

Nitromethane - Fluorination of decalin in nitromethane gave many products which could not be identified, a significant amount of tar, and some *cis*-9-fluorodecalin **(47)** (33% yield).

The preliminary solvent study showed that, of all the reaction media considered, only nitrile solvents facilitate selective fluorination. Consequently, this solvent was investigated further as a reaction medium and the reactions which were carried out are detailed in Scheme 2.4 and Table 2.2.



(46)

i - 4-5 equiv. 10% F_2/N_2, solvent, 0°C

Scheme 2.4

Solvent System	***cis*-9-Fluorodecalin (47) Yield (Conv.)[a] %**	**Tar %**
Acetonitrile	57 (64)	0
Acetonitrile-Trichlorotrifluoroethane[b] (1:4)	56 (63)	0
Acetonitrile-Trichlorotrifluoroethane[b] (1:9)	52 (92)	0
Acetonitrile-Trichlorotrifluoroethane[b] (1:19)	27 (40)	0
Acetonitrile-DCM (1:19)	0 (2)	0

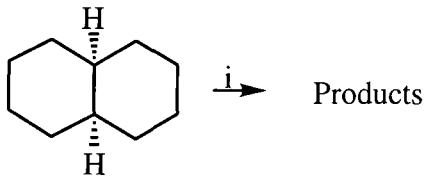
Table 2.2

[a] After work-up.
[b] Freon 113.

Description of Table 2.2 - Solutions which comprised of 5, 10 and 20% (v/v) acetonitrile in 1,1,2-trichlorotrifluoroethane were prepared and explored as reaction media and the amount of *cis*-9-fluorodecalin **(47)** obtained in these reactions increased as the relative amount of acetonitrile was increased.

Starting material (98%) was recovered after passing fluorine through a mixture of decalin (**47**) and 5% (v/v) acetonitrile-dichloromethane.

The affect of *p*-dinitrobenzene, a radical inhibitor, on the fluorination reaction was investigated as shown in Scheme 2.5 and the results are shown in Table 2.3.



(46)

i - 4-5 equiv. 10% F_2/N_2, CH_3CN, *p*-dinitrobenzene, 0°C

Scheme 2.5

Solvent System	***cis*-9-Fluorodecalin (47) Yield (Conv.)[a] %**	**Tar %**
Acetonitrile fluorine:substrate = 5:1	57 (64)	0
Decalin-Dinitrobenzene = 50:1*	60 (83)	0
Decalin-Dinitrobenzene = 20:1*	65 (77)	0
Decalin-Dinitrobenzene = 13:1*	66 (85)	0

Table 2.3

* mol : mol ratio; approx. 2, 5 and 8 mol% respectively.

[a] After work-up.

Table 2.3 shows that addition of *p*-dinitrobenzene to the reaction mixture does not alter significantly the amount of *cis*-9-fluorodecalin (**47**) produced in the reaction.

2.3.2 Conclusions from solvent survey

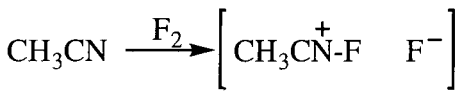
A range of fluorination reaction media has been investigated and it was found that nitrile solvents promote selective fluorination of a model hydrocarbon compound.

Direct and selective fluorination is, in theory, only possible when reaction conditions encourage elemental fluorine to act as an electrophile and it is clear that nitrile solvents can achieve this.

Acetonitrile is a relatively polar solvent ($\varepsilon = 36.6$)[109] and may stabilise a polar transition state via dipole-dipole interactions. However, if such interactions determine the selectivity of the fluorination reaction it is reasonable to expect that

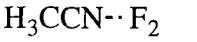
nitromethane ($\varepsilon = 37.3$)[109] would also promote selective fluorination. It is likely, therefore, that the dielectric constant of the fluorination medium is not the sole factor which controls the selectivity of the reaction.

Acetonitrile may form a loose N-F type complex (Scheme 2.6) which has a transient existence and a recent study by Legon[110] supports this postulation.



Scheme 2.6

Legon mixed fluorine and acetonitrile in a FT-microwave spectrometer and determined the rotational spectrum of a fluorine-acetonitrile complex. It was concluded that the complex was bound weakly and of the form shown in Scheme 2.7.



Scheme 2.7

The following experiment was designed to prove (or otherwise) that any complex of this type had a very short lifetime.

Elemental fluorine, as a 10% mixture with nitrogen, was passed through stirred, cooled (0°C) acetonitrile and, after addition of all the fluorine, anisole was added. The resulting mixture was stirred for 30 minutes and, after a standard aqueous work-up, gave a crude product which contained anisole (98 area %), *o*-fluoroanisole (1 area %) and *p*-fluoroanisole (1 area %).

This result can be rationalised using a number of explanations, which are:

- The fluorine-acetonitrile complex suggested above exists for only a short period of time.
- No such association ever exists.
- Acetonitrile co-ordinates with elemental fluorine after the substrate has formed an association with the halogen.

It is interesting to note that using a reaction medium which consists of acetonitrile and either dichloromethane or 1,1,2-trichlorotrifluoroethane results in a reaction which is less selective than the corresponding reaction which is carried out in acetonitrile only. Both dichloromethane and trichlorotrifluoroethane have a lower dielectric constant than acetonitrile and, therefore, it is possible that both the dielectric constant of the reaction medium and formation of an N-F type complex are required for selective fluorination.

In summary, the solvent survey highlighted that nitrile solvents promote selective direct fluorination of decalin and the reasons for this are not understood fully.

2.4 Fluorination of hydrocarbon compounds using elemental fluorine

2.4.1 Fluorination of both cyclic and acyclic hydrocarbon compounds

Having established that acetonitrile promotes the selective direct fluorination of *cis*-decalin (**46**), the fluorination of a range of hydrocarbon compounds was performed to determine the scope of the reaction.

All fluorination reactions which are discussed in this section were performed as described above (Scheme 2.8) and the results are shown in Table 2.4.

$$RH \xrightarrow{i} RF$$

i - 10% F_2/N_2, CH_3CN, 0°C.

Scheme 2.8

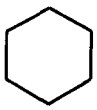
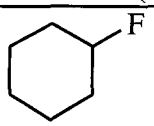
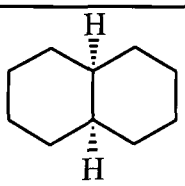
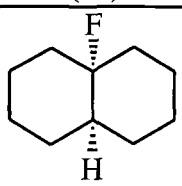
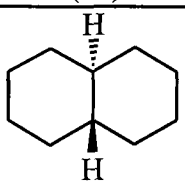
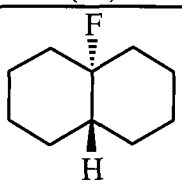
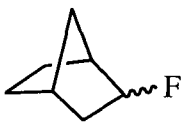
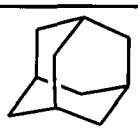
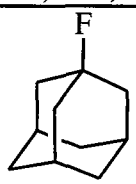
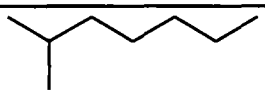
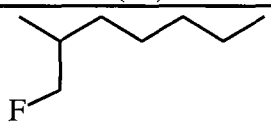
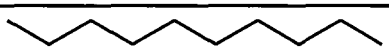
Substrate	Major Product(s)	Yield (Conv.) /%
 **(36)**	 **(37)**	63 (53)
 **(46)**	 **(47)**	57 (64)
 **(48)**	 **(49)**	54 (68)
 **(41)**	 *exo : endo* = 5:1[a] **(43A, 43B)**	41 (60)
 **(39)**	 **(44)**	65 (70) + 2-fluoroadamantane 11
 **(50)**	 + 1-fluoro-6-methylheptane product ratio = 2:1 respectively[a] **(51A, 51B)**	24 (81)
 **(52)**	2-, 3-, 4-, and 5-fluorodecane product ratio = 1: 1: 1: 3[a] **(53A-12D)**	63 (61)

Table 2.4

[a] - Isolated and characterised as an isomeric mixture.

Products were purified by preparative scale GC except 1-fluoroadamantane (**44**) which was purified by column chromatography on silica gel using 6:1 cyclohexane-dichloromethane as the eluent. All pure products were characterised using NMR and IR spectroscopies, mass spectrometry, melting point or boiling point determination (where appropriate), elemental analysis and, where possible, by comparison with literature reported data (references are given in the experimental section of this Chapter).

It was found that the amount of by-products produced in all reactions increased as the conversion was increased and, therefore, conversion values were kept between approximately 50 and 80%. However, reaction conditions were not fully optimised and it is likely that all yields could be improved.

Some difficulty was experienced when extracting the products from the reaction mixture and it is suspected that handling losses could be reduced if reactions were attempted on a larger scale.

The crude product mixtures decomposed extensively when stored at room temperature and, therefore, all crude products were kept at -10°C prior to purification.

Most crude product mixtures contained very few by-products and typical by-products included the corresponding difluorinated alkane, polyfluorinated alkane and alkene. However, a large number of products (which could not be identified) were observed in both the decane (**52**) and 2-methyheptane (**50**) crude mixtures and this will be discussed in more detail in the following text.

Fluorocyclohexane (37) - The passage of gaseous reagent through the cyclohexane (**36**) reaction mixture promoted cyclohexane (**36**) and/or fluorinated products to evaporate and, consequently, this reaction was carried out with a cold trap placed between the outlet of the reaction vessel and the inlet to the soda lime tower. After addition of all the fluorine to the reaction mixture, the contents of the cold trap and the reactor were combined and then treated as stated in the general procedure above.

***cis*- and *trans*-9-Fluorodecalin (47, 49)** - Direct fluorination of both *cis*- and *trans*-decalin proceeds with retention of stereochemistry and this is consistent with the results obtained by Rozen[108].

In general, tertiary C-H bonds are more electron rich than secondary because the alkyl group donates electron density and, therefore, fluorination of both decalin molecules occurs at the most electron-rich C-H bond in the molecule.

***exo*- and *endo*-2-Fluoronorbornane (43A, B)** - Fluorination of norbornane was attempted as detailed in the general procedure above but only a trace amount of material was obtained in the crude product. It was found that norbornane (**41**) and most norbornane derived products were subliming from the product mixture while the

solvent was being removed by distillation. Consequently, after elemental fluorine was passed through a mixture of norbornane (**41**) and acetonitrile, the mixture was poured into iced water and the resulting solid was removed by filtration to give the crude product.

The ^{19}F NMR spectrum of the pure mixture contained two isolated peaks which were present in the ratio of *ca.* 1 : 5 and, therefore, indicates (in conjunction with the GC-MS of the mixture) that the mixture consisted of two monofluorinated norbornyl derivatives. The ^{13}C NMR spectrum contained two peaks at δ_C = *ca.* 95 ppm which both display a coupling constant of *ca.* 180Hz and these data indicate the presence of two CHF carbon types. NMR data were used to ascertain that the mixture contained both *exo*- and *endo*-2-fluoronorbornane (**43A, B**) and the spectral data of the major isomer match spectral data which have been reported in the literature[111] for *exo*-2-fluoronorbornane (**43A**) .

The C-2 carbon-hydrogen bonds in norbornane (**41**) have the highest p-orbital character of all the C-H bonds in the molecule and, therefore, fluorination of this substrate occurs at the C-H bonds which are the most electron rich.

2-*exo*-Fluoronorbornane (**43A**) is more thermodynamically stable than the corresponding *endo*-isomer (**43B**) because there is less steric crowding. Therefore, fluorination of norbornane gives a predominance of the 2-fluoronorbornane isomer which has the greatest thermodynamic stability.

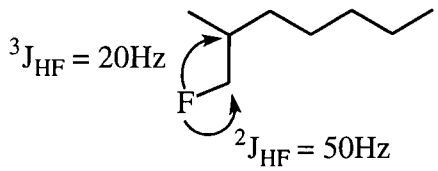
1-Fluoroadamantane (44) - Table 2.4 shows that both 1- and 2-fluoroadamantane were obtained upon reaction of elemental fluorine with adamantane. 1-Fluoroadamantane (**44**) was isolated, whereas, 2-fluoroadamantane was not and, therefore, the identity of this compound was postulated using both mass spectral and ^{19}F NMR data.

1-Fluoro-2-methylheptane (51A) and 1-fluoro-6-methylheptane (51B) - The crude product from this reaction contained at least four isomers (by GC) of fluoromethylheptane (65 area %) and many (>20) other products which could not be identified. The ^{19}F NMR spectrum of the mixture contained six major peaks in the region of $-\delta_F$ = 135 -220 ppm.

Preparative scale GC was used to isolate the major product (by GC) from the crude mixture and the ^{19}F NMR spectrum of the product contained two multiplet peaks in the ratio of 1 : 2. Therefore, the GC peak which was isolated represents two isomers of fluoromethylheptane which co-elute from the GC column.

The identity of the isolated products was determined using NMR spectroscopy. The ^{19}F NMR spectrum of the pure isomeric mixture contains a major and a minor peak which both have a chemical shift ($-\delta_F$ = *ca.* 220 ppm) in the CH_2F region of the spectrum. The major signal appears as a double triplet (J = *ca.* 20Hz and 50Hz respectively) (Scheme 2.9) and the minor as a multiplet. The ^{13}C NMR

spectrum contains two peaks which are both characteristic of CH_2F and all other spectroscopic data were consistent with 1-fluoro-2-methylheptane (**51A**) as the major isomer and 1-fluoro-6-methylheptane (**51B**) as the minor.



Scheme 2.9

It is likely that the low yield shown in Table 2.4 resulted because many other monofluorinated products were produced in the reaction.

It is not understood why the major product from this reaction is 1-fluoro-2-methylheptane (**51A**) given that all of the above fluorination reactions proceed at the most electron rich C-H bond(s) in the molecule. It could be argued that the most electron-rich bond in the molecule, the tertiary carbon-hydrogen bond, is relatively sterically hindered by two methyl groups and an alkyl chain which can twist back and shield the tertiary C-H site from attack. However, not less than six major fluorinated products were observed in the crude product mixture from this reaction and the 'major' product was in a very small excess relative to all other products. It is suggested that reaction of elemental fluorine with 2-methylheptane (**50**) results in fluorination of almost all the C-H bonds in the molecule as there is not a single favoured site for reaction when both steric and electronic factors are taken into consideration.

2-, 3-, 4-, and 5-Fluorodecane (53A-D) - The ^{13}C NMR spectrum of the four fluorodecane isomers (which were isolated as a mixture) contains four peaks in the CHF region of the spectrum (*ca.* 80-90 ppm) which all display a one-bond carbon-fluorine coupling constant (approximately 200Hz). The ^{19}F NMR spectrum contains four isolated multiplets and all other spectral data are consistent with the structures shown in Table 2.4.

Unfortunately, it is not possible to assign spectral data to each isomer in the mixture and, therefore, it is not possible to report the relative ratio of each fluorinated isomer.

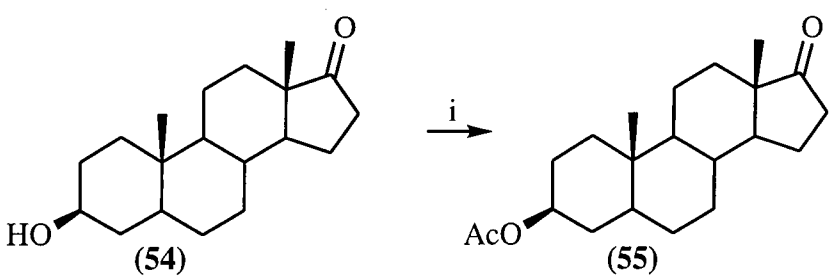
In contrast to the direct fluorination of the cyclic hydrocarbon compounds described above, the crude product from this reaction contained many compounds which could not be identified. It is possible that these products may include difluorodecane, polyfluorodecanes, decene, and compounds which are derived from skeletal rearrangement and fragmentation processes.

Decane (**52**) contains six types of C-H bonds and the five types of secondary C-H bonds have a similar electron density. The terminal C-H bonds have a lower electron density than the secondary ones and, therefore, fluorination of decane occurs predominantly at the most electron rich C-H bonds.

It should be noted that a small amount (<10%) of 1-fluorodecane (**53E**) was also observed (^{19}F NMR) in the crude product and this suggests that primary site fluorination may not be beyond the scope of the fluorination methodology.

2.4.2 Fluorination of 3β-Acetoxy-5α-androstan-17-one (55)

3β-Hydroxy-5α-androstan-17-one (**54**) is available commercially and was converted to 3β-acetoxy-5α-androstan-17-one (**55**) by stirring a solution of the steroid substrate, acetic anhydride, and a catalytic amount of 4-dimethylaminopyridine (DMAP) in dichloromethane (Scheme 2.10). This transformation was required to protect the hydroxyl group from oxidation upon reaction of the steroid with elemental fluorine.



(54) (55)

96%, 100% conv.

i = Ac_2O, DMAP, DCM, r.t., 2 h.

Scheme 2.10

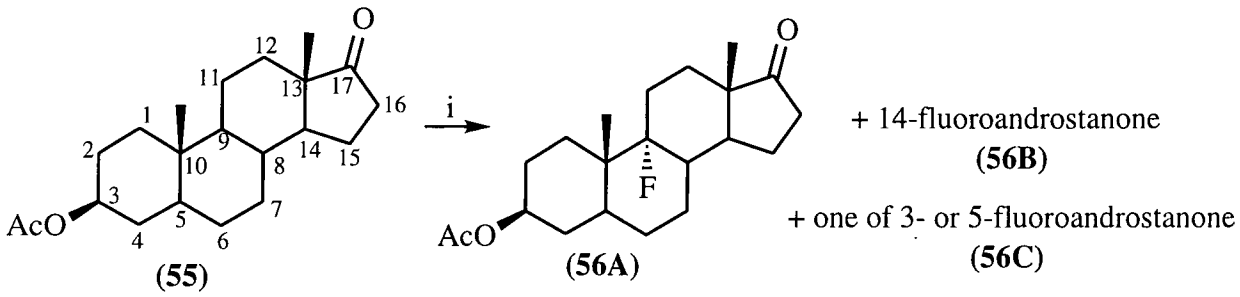
Fluorination of acetoxyandrostanone (**55**) gave, after the usual work-up, a crude product mixture which contained starting material (59 area %)* and three isomers of monofluorinated starting material (31 area %)* in the ratio of 1.0 : 1.1 : 1.4 (by ^{19}F NMR). Small amounts of an unsaturated acetoxyandrostanone derivative (2 area %)*, and a trace amount of difluorinated starting material (<1 area %)* were also observed.

Standard purification techniques failed to separate the major products but, instead, their identity was postulated using the splitting patterns of the ^{19}F NMR spectrum of the crude mixture.

It was assumed that substitution of only tertiary C-H bonds had occurred (*cf.* decalin fluorination) and that the fluorine atoms in the steroid molecule couple to all protons which are three bonds away according to the usual pattern[112] i.e. $^3J_{HF}$ (*trans*)

* Approximate values.

= 30-60 Hz; (*cis*) = 0-20 Hz. Using these assumption the fluorinated isomers were identified as 3β-acetoxy-9-, 14- and one of 3- or 5-fluoro-5α-androstan-17-one (**56A-C**) (Scheme 2.11).



(55) (56A)

i = 10% F_2/N_2, CH_3CN, 0°C. *ca.* 76%, 41% conv.

Scheme 2.11

2.4.3 Summary of results

Using the direct fluorination methodology which has been developed in this Chapter, a range of cyclic hydrocarbon compounds have been selectively fluorinated in reasonable yield. Fluorination occurs at the most electron-rich carbon-hydrogen bond(s) in the substrate molecule and with retention of configuration.

Direct fluorination of straight-chain hydrocarbon compounds was less selective but substitution of the most electron-rich C-H sites did occur. In contrast, fluorination of a branched chain hydrocarbon compound was not selective and, at present, it is not understood why.

It is highly likely that the fluorination methodology detailed in this Chapter could be used to selectively fluorinate a wide range of cyclic and straight chain hydrocarbon compounds but fluorination of branched chain substrates requires further investigation.

2.4.4 Postulation of the mechanism of fluorination

In principle, the above fluorination reactions may proceed via a radical, a single electron transfer (SET) or an aliphatic electrophilic substitution type pathway and each of these possibilities will now be considered.

Radical fluorination mechanism - in general, direct fluorination of the hydrocarbon compounds discussed above occurs at the most electron-rich C-H bond of the substrate and this observation could be explained by a radical fluorination pathway. The fluorine atom, which is relatively electrophilic, reacts with substrates at the site which is the most electron rich (usually, tertiary C-H > secondary C-H >

primary C-H) but it is very unlikely that these reactions proceed via a radical mechanism for the following reasons which are:

- The selectivity of the reactions far exceeds the selectivity of fluorine atom reactions (Chapter 1).
- Fluorination of *cis*-decalin (**46**) was not altered by the addition of a radical inhibitor.
- Regardless of the details of a radical fluorination mechanism, it is likely that reaction would progr

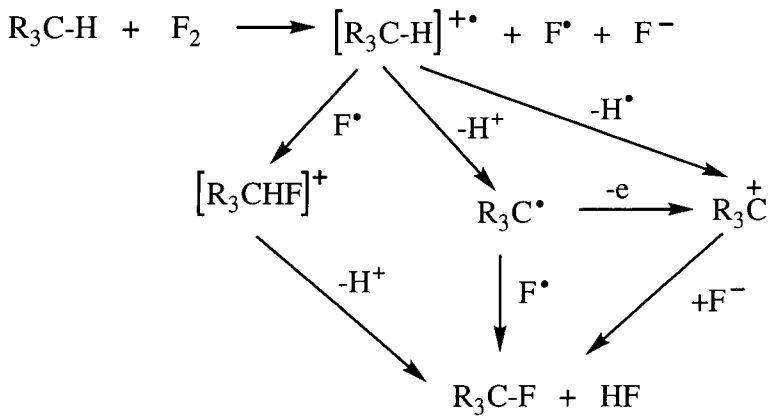
ess through an intermediate which has trigonal planar geometry (Scheme 2.12). Fluorination of such a species would not necessarily give a product which has the same stereochemistry as the starting material. For example, fluorination of both *cis*- and *trans*-decalin (**46, 48**) would give the more thermodynamically stable *trans*-9-fluorodecalin (**49**) but not products with retention of configuration as was observed.

$$R_3C\text{-}H + F_2 \longrightarrow R_3C\text{-}F + HF$$

intermediate

Scheme 2.12

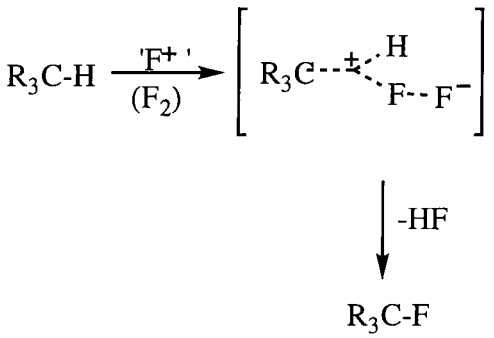
SET process - SET involves initial oxidation of the hydrocarbon substrate, which is relatively electron rich, to give a fluorine atom, fluoride ion and a radical carbocation. (Scheme 2.13) These species could then react in a number of different ways, such as those shown in Scheme 2.13, to give monofluorinated product.



Scheme 2.13

In this process, a radical or a radical-cation or a cation reacts with a fluorine atom or fluoride ion and, therefore, this type of mechanism would not necessarily give a product which has the same stereochemistry as the starting material. On this basis alone it can be reasoned that the fluorination reactions do not proceed via a SET process.

Aliphatic electrophilic substitution - both Barton[51] and Rozen[48] proposed that the direct fluorination of some hydrocarbon compounds (and hydrocarbon derivatives) proceeds via an aliphatic electrophilic substitution (S_E2) pathway and the results of this study are also consistent with this proposal. (Scheme 2.14)



Scheme 2.14

Reaction of 'electrophilic fluorine' with the substrate results in formation of a pentacoordinate transition state which collapses to give fluoroalkane and hydrogen fluoride. This type of mechanism is relatively rare but well accepted and gives products which have the same stereochemistry as the starting material.[113]

2.5 Investigation of the mechanism of fluorination

2.5.1 Introduction

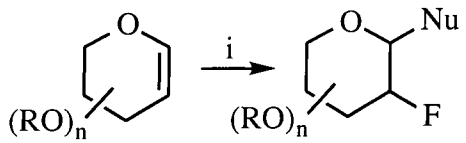
Having postulated that the above fluorination reactions proceed via an aliphatic electrophilic substitution mechanism we attempted to gain information which would support this hypothesis and the next part of this Chapter details our attempts to do so.

Many N-F fluorinating agents are available commercially[93] and, at the time that this study was carried out, Selectfluor™ was one of the least expensive (1g costs *ca.* £1 and contains 5% fluorine). The selective fluorination of many organic compounds has been effected using Selectfluor™ (Section 1.6.2; page 36) and in a small number of cases the mechanism of the fluorination reaction was also investigated.

In the following section we will use Selectfluor™ to gain some information about the elemental fluorine reactions which were described in the last section.

Consequently, what follows is a brief review of the studies which have investigated the mechanism of fluorination reactions which involve Selectfluor™.

Wong and co-workers[114] have demonstrated that Selectfluor™ reacts with various glycal compounds in the presence of a nucleophile to give 2-fluoroglycoside derivatives (Scheme 2.15) and, to understand these reactions, Wong carried out a mechanistic study using a radical probe (**57**).

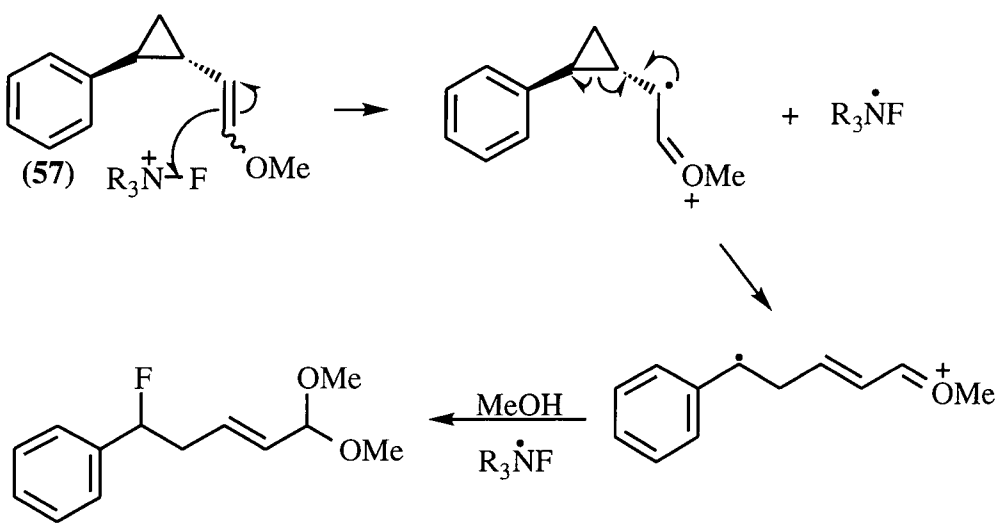


R = Ac, H, etc.
Nu = R_1O, R_2NH, R_3S

i = 1) 1.1 Selectfluor™, CH_3NO_2, molecular sieves, Ar atmosphere, 6 h, r.t.
2) 1.1 NuH-CH_3NO_2, 100°C, 1 h.

Scheme 2.15

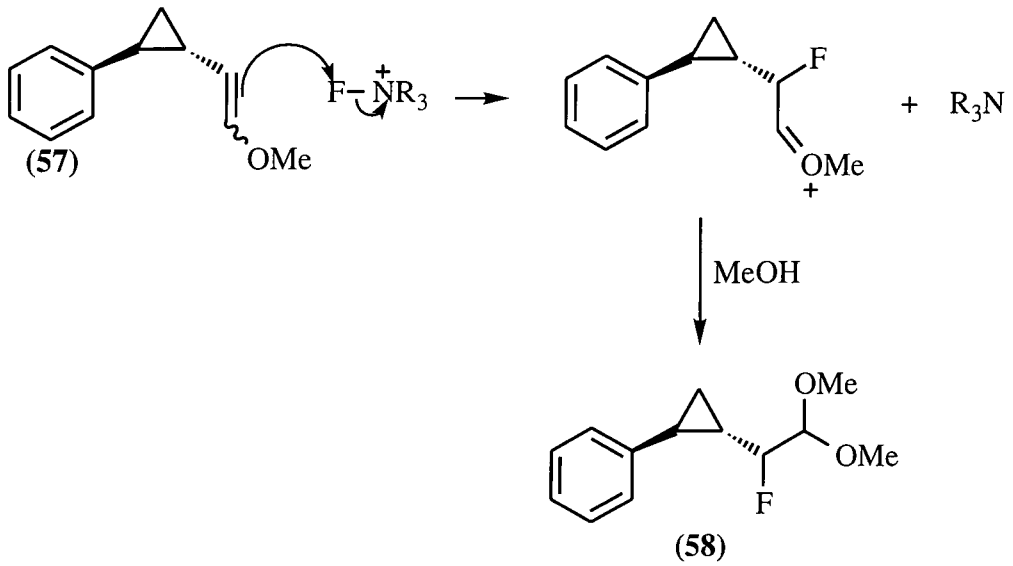
It was reasoned that fluorination via a one electron transfer process would result in a radical site next to the cyclopropane ring and subsequent opening of the ring as shown (Scheme 2.16).



Scheme 2.16

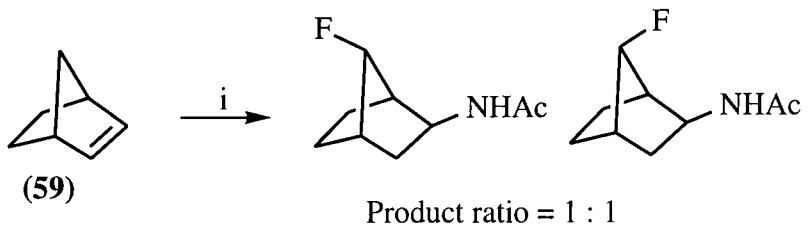
Alternatively, an electrophilic mechanism (two electron transfer process) would proceed as shown in Scheme 2.17.

Reaction of the radical probe with Selectfluor™ gave only **58** and this suggests that fluorination proceeds via a two electron transfer pathway.



Scheme 2.17

Zupan[115] used bicyclo[2.2.1]heptene (**59**) as a mechanistic tool and found that reaction of this molecule with Selectfluor™ in acetonitrile gave products which are indicative of an electrophilic fluorination mechanism. (Scheme 2.18)

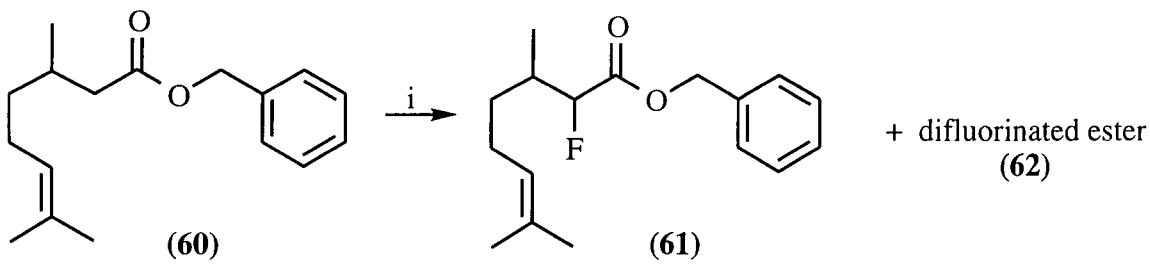


Product ratio = 1 : 1

i = 1.2 Selectfluor™, CH_3CN, 4 h, r.t.

Scheme 2.18

Differding[116] has shown that the enolate of citronellic ester (**60**) reacts with various N-F fluorinating agents (and xenon difluoride) to give products (**61**) and (**62**) which are derived from a two electron transfer process. (Scheme 2.19)



(60) (61)

i = 1) Base, THF, -78°C.
2) N-F reagent, -78°C - r.t.

Scheme 2.19

In summary, all of the above mechanistic studies have shown that Selectfluor^{TM} (and various fluorinating agents which are closely related) promote selective fluorination via an electrophilic mechanism.

Based on the results of these studies, we believe that Selectfluor^{TM} could, in principle, promote the fluorination of hydrocarbon compounds via an aliphatic electrophilic substitution mechanism and, consequently, the objective of the work outlined in the next part of this Chapter was two fold. Firstly, we aimed to perform the fluorination of the hydrocarbon compounds that are described in Section 2.1 using Selectfluor^{TM} and, secondly, we aimed to compare the product distributions obtained from these reactions with those obtained from the corresponding elemental fluorine reaction.

We reasoned that if the elemental fluorine and Selectfluor^{TM} product distributions are very similar (for the same substrate) then it is likely that both fluorinating agents promote fluorination via the same type of pathway, namely an electrophilic mechanism.

2.5.2 Fluorination of hydrocarbon compounds using Selectfluor^{TM}

Fluorination of cyclohexane (**36**), decalin (**46, 48**), norbornane (**41**), adamantane (**39**), and decane (**52**) using Selectfluor^{TM} as the fluorinating agent will now be described and a full comparison of the Selectfluor^{TM} and elemental fluorine product distributions will be given in Section 2.5.4 (page 69).

All reactions were performed by heating (82°C)* a mixture which contained the substrate, Selectfluor^{TM}, and acetonitrile and gave, after a standard aqueous work-up, a crude product mixture which was analysed by GC-MS and ^{19}F NMR (using a

* In all cases, no reaction was evident (by ^{19}F NMR) below 82°C.

fluorobenzene reference). Yield and conversion values were calculated as for the direct fluorination reactions.

The number of by-products produced in the fluorination reactions increased as the reaction time was increased and, therefore, reactions were followed (by ^{19}F NMR and in some cases TLC) and were terminated so as to minimise the number of by-products produced but maximise the conversion of the reaction.

Crude products were not purified (unless stated otherwise) but instead the major products obtained were identified by comparison with authentic samples (prepared using elemental fluorine). The results of these experiments are shown (Scheme 2.20 and Table 2.5).

$$RH \xrightarrow{i} RF$$

i - Selectfluor^{TM}, CH_3CN, 82°C.

Scheme 2.20

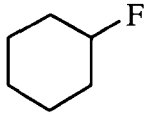
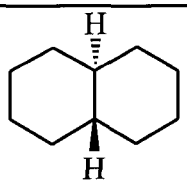
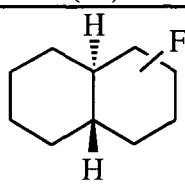
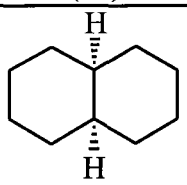
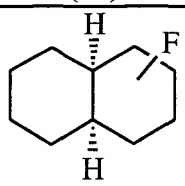
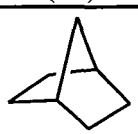
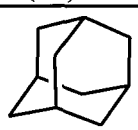
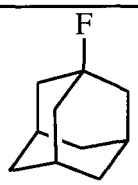
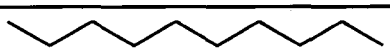
Substrate	Reaction Time h	Major Product(s)	Yield (Conv.) %
 **(36)**	26	 **(37)**	21 (99)
 **(48)**	3.5	 **(63)**	80 (41)
 **(46)**	1.5	 **(64)**	58 (61)
 **(41)**	5	no reaction	-
 **(39)**	3	 **(44)**	68 (73) + 2-F-adamantane *ca.* 12%
 **(52)**	16	2-, 3-, 4-, and 5-fluorodecane product ratio = 1: 1: 1: 2 **(53A-D)**	58 (84)

Table 2.5

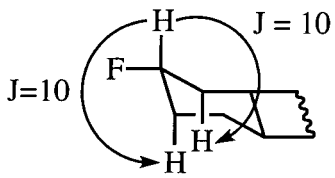
Fluorocyclohexane (37) - It is likely that some starting material and fluorinated cyclohexane, which are both volatile, evaporated during the course of the reaction and that this led to the low yield and high conversion values which were obtained.

***trans*-1- and 2-Fluorodecalin (63)** - Initially, the identity of the major fluorinated products from this reaction was not known (the product mixture did not

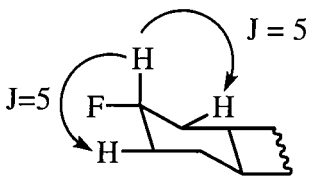
contain *trans*- or *cis*-9-fluorodecalin (**49, 47**) (by ^{19}F NMR)) and, therefore, a pure isomeric mixture of *trans*-fluorodecalin was separated from the crude product using preparative scale GC. The pure isomeric mixture was characterised using standard techniques and the exact structure of the products was elucidated using the ^{1}H, ^{13}C, ^{19}F , DEPT and HSQCTOCSY NMR spectroscopy.

The ^{13}C NMR spectrum of the fluorodecalin mixture contains four peaks at δ_C= *ca.* 90 ppm and each of these peaks is split by a coupling constant of *ca.* 200Hz and these data are consistent with the presence of four CHF carbon types.

The CHF proton in each isomer was readily identified in the ^{1}H NMR spectrum of the mixture as they appear at a chemical shift (*ca.* 5 ppm) and with a coupling pattern which is highly characteristic. Each CHF proton was observed as a double multiplet; the doublet was due to a two bond HF coupling and the multiplet to coupling with adjacent protons. Each CHF proton in each isomer displays a unique splitting pattern and this pattern was used to gain information about each isomer. For example, the double triple triplet (J = *ca.* 49, 10 and 5Hz respectively) centred at *ca* 5 ppm (NMR spectrum no. 4) was assigned to *trans*-2-fluoro$_{(eq)}$decalin (**63A**) by considering the value of the coupling constants (Scheme 2.21).



two three-bond H_a-H_a couplings

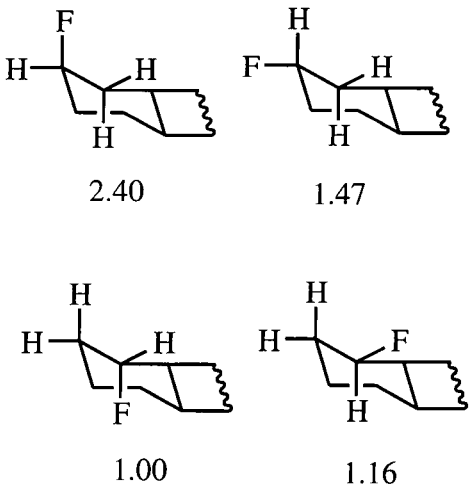


two three-bond H_a-H_{eq} couplings

(J values are given in Hz)

Scheme 2.21

An HSQCTOCSY NMR experiment was used to identify (most of) the ^{13}C NMR signals which represented each isomer and all spectroscopic data are consistent with the structures shown (Scheme 2.22). The relative ratio of each isomer was calculated (^{19}F NMR) and is also shown.



2.40 1.47

1.00 1.16

Scheme 2.22

Scheme 2.22 shows that fluorination of *trans*-decalin (**48**) occurs at position-1 and -2 of the molecule in the ratio of 2.2 : 3.9 respectively and this is an unexpected result. The tertiary sites of *trans*-decalin (**48**) are the most electron-rich bonds in the molecule and, consequently, the most favoured for fluorination. However, fluorination of *trans*-decalin (**48**) using Selectfluor^{TM} proceeds according to the relative availability of all three types of carbon in the molecule i.e. pos-2> pos-1> pos-9. It is likely that this pattern of substitution has resulted because the Selectfluor^{TM} molecule is relatively sterically demanding.

***cis*-1- and -Fluorodecalin (64)** - A pure isomeric mixture of *cis*-fluorodecalin (**64**) (58%, 61% conv.) was prepared, purified, and characterised as for *trans*-fluorodecalin (**63**) (detailed above) and neither *cis*- nor *trans*-9-fluorodecalin (**47, 49**) were present in the pure isomeric mixture.

The ^{1}H, ^{13}C and ^{19}F NMR spectra of the pure isomeric mixture which were acquired at room temperature contained only large, broad peaks which were of no diagnostic use. Spectra which were obtained at -57°C contained peaks which were sharp and well defined but, unfortunately, the ^{13}C NMR spectrum obtained at this temperature was very complex due to the large number of peaks which it displayed and it was not analysed further. It was noted, however, that at least four types of CHF carbon were present in the mixture and this was substantiated by the fact that the ^{19}F NMR spectrum of the product mixture at -57°C contained four signals.

The ^{1}H NMR spectrum of the mixture at -57°C contained a large number of signals which were partially superimposed and spectral data (^{1}H, ^{13}C or ^{19}F) could not be used to prove the presence of *cis*-1- and 2-fluorodecalin in the pure mixture. However, spectral and GC-MS data clearly demonstrate that the mixture contained

four types of monofluorinated *cis*-decalin (**46**) and that 9-fluorodecalin (**47, 49**) was not present.

Given this information, and the fact that *trans*-decalin gave a mixture of *trans*-1- and 2-fluorodecalin upon reaction with Selectfluor^{TM}, all evidence is consistent with formation of *cis*-1-fluoro$_{(eq)}$decalin (**64A**), *cis*-1-fluoro$_{(ax)}$decalin (**64B**), *cis*-2-fluoro$_{(eq)}$decalin (**64C**), *cis*-2-fluoro$_{(ax)}$decalin (**64D**).

Attempted fluorination of norbornane (41) - Heating (82°C) a mixture which contained norbornane, Selectfluor^{TM}, and acetonitrile promotes norbornane (**41**) to sublime into the condenser of the experimental apparatus and, consequently, only starting material was recovered after a work-up.

This reaction was also attempted in a sealed tube but, again, only starting material was recovered.

1-Fluoroadamantane (44) - Table 2.5 shows that both 1- and 2-fluoroadamantane were obtained upon reaction of Selectfluor^{TM} with adamantane (**39**). 1-Fluoroadamantane (**44**) was isolated by column chromatography on silica gel using 6:1 cyclohexane-dichloromethane as eluent and, therefore, the yield shown in Table 2.5 corresponds to pure, isolated fluoroadamantane. 2-Fluoroadamantane was not isolated and the identity of this compound was postulated using mass spectral and ^{19}F NMR data.

2-, 3-, 4-, and 5-Fluorodecane (53A-D) - It is interesting to note that 1-fluorodecane (**53E**) was not observed (by ^{19}F NMR) in the crude product mixture from this reaction but many (> 20) products which could not be identified were present. It is likely that these product include di- and polyfluorinated decane, decene, and compounds which are derived from skeletal rearrangement or scission processes.

General points - Very few difluorinated products were observed in the crude product mixtures from the above Selectfluor^{TM} reactions. This indicates that the presence of one fluorine atom in the hydrocarbon structure deactivates the molecule to further fluorination.

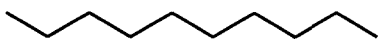
With the exception of the decalin examples, fluorination occurs at the most electron-rich C-H bond of the substrate molecule.

2.5.3 Attempted fluorination of decane using other fluorinating reagents

So far, only elemental fluorine and Selectfluor^{TM} have been used as fluorinating agents in this study. For comparison and in order to gain information about the direct fluorination reactions, we have attempted the fluorination of a model hydrocarbon compound (decane) using a sample of other fluorinating reagents which are also available commercially.

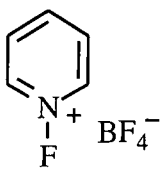
Fluorination of decane (**52**) was attempted using xenon difluoride, N-fluoropyridinium tetrafluoroborate (NFPY), and N-fluorobenzenesulfonimide (NFSI), because previous reports (discussed in Section 2.5.1; page 58) have demonstrated that these reagents can promote selective fluorination via a two electron transfer process. Therefore, if the product distributions obtained using these reagents are similar to those obtained when using elemental fluorine, it is likely that elemental fluorine also promotes fluorination via this mechanism.

Reactions were attempted in accordance with Scheme 2.23* and, after the usual work-up, gave a crude product mixture which was analysed by ^{19}F NMR (with reference to fluorobenzene) and GC-MS. (Table 2.6)



(52)

i = 1.1 equiv. fluorinating agent, CH_3CN, 82°C.

NFSI = $FN(SO_2Ph)_2$ NFPY = 

Scheme 2.23

* In all cases, no reaction was evident (by ^{19}F NMR) at a reaction temperature below 82°C.

Fluorinating Agent	Time	Yield (conversion) %	53A : 53B : 53C : 53D : 53E
Elemental Fluorine	10% F_2 (0°C)	63 (61)	1.0 : 1.1 : 1.2 : 2.6 : 0.4
Selectfluor™	16 h	58 (84)	2.4 : 1.3 : 1.0 : 1.1 : 0
NFSI	16 h	no reaction	-
NFSI	3.5 d	49 (21)	1.3 : 1.0 : 1.0 : 1.1 : 0
NFPY	16 h	no reaction	-
NFPY	3.5 d	no reaction	-
XeF_2	16 h	47 (57)	1.5 : 1.0 : 1.3 : 1.6 : 0.5

Table 2.6

Discussion of Table 2.4 - All reactions (except with elemental fluorine) were carried out by heating the reaction mixture for 16 hours as this facilitated comparison with the Selectfluor™ reaction. If reaction was not observed after this time, the experiment was repeated for 3.5 days. Elemental fluorine, Selectfluor™, NFSI, and xenon difluoride all effect the fluorination of decane (**52**) in reasonable yield but it was noted that reaction of NFSI with decane (**52**) was particularly sluggish (only 21% conversion was observed after 3.5 days).

The final column of Table 2.4 displays the ratio of monofluorinated products which was observed in the crude product. **53A** to **53D** have ^{19}F NMR chemical shift values of -173.42, -181.36, -181.69, and -182.66 ppm respectively and have been isolated as a mixture and characterised as 2-, 3-, 4- and 5-fluorodecane (not necessarily respectively). **53E** was not isolated but represents a product which has a ^{19}F NMR chemical shift and splitting pattern identical to 1-fluorodecane.

53E was absent from all crude products except those which were prepared using either elemental fluorine or xenon difluoride. This suggests that these reagents provide an electrophile which has sufficient power to fluorinate the primary sites in decane.

In general, all reactions gave product distributions which are very similar and, based on the proposed theory that similar product distributions result from similar

mechanisms, it is likely that all these fluorination reactions proceed via a two electron transfer process.

Regardless of mechanism, the relative fluorinating powers of the reagents considered in this study is as follows:

Elemental fluorine / Xenon difluoride > Selectfluor^{TM} > NFSI > NFPY

2.5.4 Fluorination using both Selectfluor^{TM} and elemental fluorine: A comparison

Table 2.7 shows a summary of some of the fluorination reactions which were discussed in Sections 2.4 and 2.5.

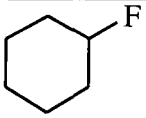
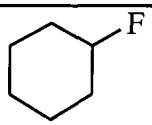
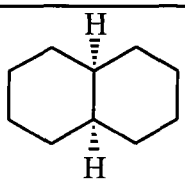
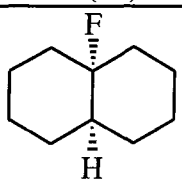
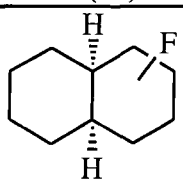
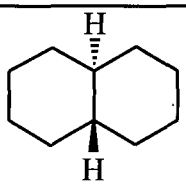
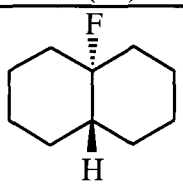
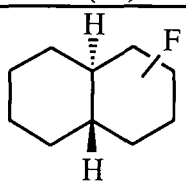
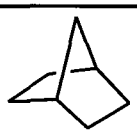
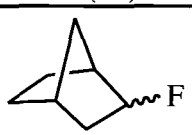
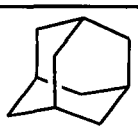
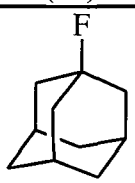
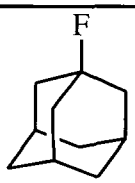
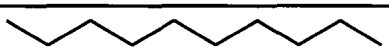
Substrate	Major Product(s) using Elemental Fluorine Yield (Conv.) %	Major Product(s) using Selectfluor™ Yield (Conv.) %
 **(36)**	 **(37)** 63 (53)	 **(37)** 21 (99)
 **(46)**	 **(47)** 57 (64)	 **(64)** 58 (61)
 **(48)**	 **(49)** 54 (68)	 **(63)** 80 (41)
 **(41)**	 **(43A, B)** 41 (60)	-
 **(39)**	 **(44)** 65 (70)	 **(44)** 68 (73)
 **(52)**	2-, 3-, 4-, and 5-fluorodecane in approx. 1: 1: 1:2.5 **(53A-D)** 63 (61)	2-, 3-, 4-, and 5-fluorodecane in approx. 1: 1: 1:2.5 **(53A-D)** 58 (84)

Table 2.7

Both elemental fluorine and Selectfluor^{TM} promote the selective fluorination of cyclohexane (**36**), decalin (**46, 48**), adamantane (**39**), and decane (**52**).

Fluorination of norbornane (**41**) was not effected using Selectfluor^{TM} because the substrate sublimed from the reaction vessel upon heating. Therefore, comparison of the norbornane results which are shown in Table 2.6 does not serve to illustrate any mechanistic differences between elemental fluorine and Selectfluor^{TM}.

Fluorination of decalin (**46, 48**) using elemental fluorine gave 9-fluorodecalin (**47, 49**), whereas, reaction of this substrate with Selectfluor^{TM} gave 1- and 2-fluorodecalin (**63, 64**). However, it is probable that these different products are not the result of mechanistic differences between elemental fluorine and Selectfluor^{TM}.

In general, for a given substrate, product distributions obtained from the Selectfluor^{TM} reactions are very similar to those obtained from the corresponding elemental fluorine reaction and, therefore, it is highly likely that these reagents promote reaction via the same mechanism. Based on the fact that several studies have demonstrated that Selectfluor^{TM} promotes fluorination via an electrophilic mechanism, it is highly likely that elemental fluorine promotes fluorination of the above hydrocarbon compounds via the proposed aliphatic electrophilic fluorination mechanism (Section 2.4.4; page 56).

2.6 Conclusions

Direct fluorination of *cis*-decalin (**46**) was performed in a range of reaction media and it was found that nitrile solvents facilitate the selective fluorination of this substrate.

Selective direct fluorination of both cyclic and acyclic hydrocarbon compounds was then effected using acetonitrile as the reaction solvent and, in general, the corresponding monofluorinated products were obtained in reasonable yield. In most cases, substitution of the most electron-rich C-H bond(s) in the substrate molecule was observed.

The selective fluorination of various hydrocarbon compounds was also performed using Selectfluor^{TM} as the fluorination agent. For a given substrate, product distributions obtained from these reactions are very similar to those obtained from the corresponding direct fluorination. The only exception to this was that reaction of elemental fluorine with decalin (**46, 48**) gave 9-fluorodecalin (**47, 49**), whereas, reaction of Selectfluor^{TM} with this substrate gave a mixture of 1- and 2-fluorodecalin (**63, 64**).

It is likely that the direct fluorination reactions which are described in this Chapter proceed via an electrophilic substitution mechanism for the following reasons which are:

- Fluorination of a given hydrocarbon by both elemental fluorine and Selectfluor^{TM} gives the same products.
- Direct fluorination of decalin **(46, 48)** proceeds with retention of stereochemistry.
- The direct fluorination of *cis*-decalin **(46)** was not altered by the addition of a radical inhibitor.
- The selectivity displayed by the fluorination reactions far exceeds that which is expected for a radical fluorination reaction.

In conclusion, methodology for the direct monofluorination of hydrocarbon compounds has been developed and investigated. This methodology involves the use of a reaction medium which is inexpensive and readily available, near ambient reaction temperatures and can be used to replace both secondary and tertiary C-H bonds. In short, it has been shown that the preparation of selectively fluorinated hydrocarbon compounds using elemental fluorine as an electrophile can be a synthetically viable procedure.

Chapter 3: Amidation of Hydrocarbon Compounds

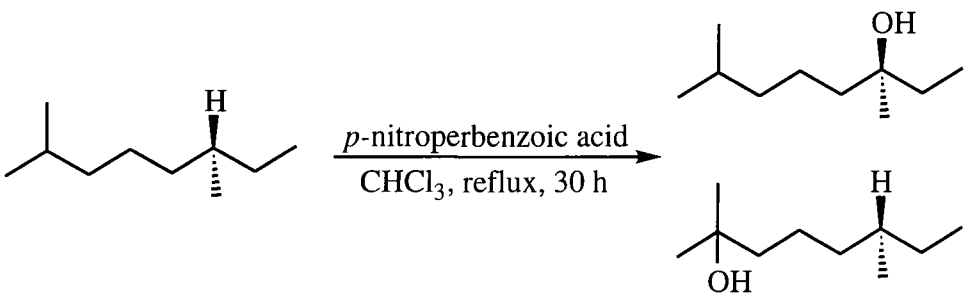
3.1 Introduction

In this Chapter a description of how an anomalous discovery led to the development of methodology for the selective functionalisation of hydrocarbon compounds will be given. The methodology involves a mixture of boron trifluoride and elemental fluorine and is an example of the use of elemental fluorine for the preparation of compounds which do not contain fluorine.

3.1.1 Selective functionalisation of hydrocarbon compounds

Since this Chapter is concerned with the selective functionalisation of hydrocarbon compounds a brief summary of the most important methods which can be used to effect such a transformation is given in the following text.

Oxyfunctionalisation of alkane compounds can be achieved using a wide range of reagents, such as molecular oxygen (autoxidation)[117], peracids[118] (Scheme 3.1) and enzymatic processes[119].



product ratio = *ca.* 2 : 1

38% conv.

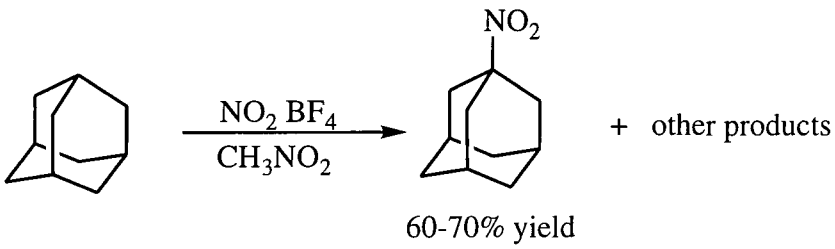
Scheme 3.1

Gif-type systems[120] which involve the use of molecular oxygen, either iron or copper, a source of electrons, acetic acid, and pyridine have been employed to convert hydrocarbon compounds to the corresponding carbonyl containing products.

However, in many oxygenation processes conversion values must be kept very low as the starting material is less susceptible to reaction than the functionalised product.

It has been shown that both highly electrophilic reagents and superacids[121,122] can be used to activate both C-H and C-C bonds in alkane compounds. Many types

of transformation, such as oxygenation, nitration (Scheme 3.2)[123], bromination, and chlorination are possible using these reagents.



60-70% yield

Scheme 3.2

Halogenation (chlorination and bromination) of alkane compounds is not usually carried out under ionic reaction conditions. In general, chloro- and bromoalkanes are prepared by direct reaction of the hydrocarbon substrate with the corresponding halogen and reaction proceeds via a free-radical pathway. Invariably, direct chlorination results in preparation of all possible monochlorinated isomers, whereas, bromination reactions are more selective.[124]

Metals, metal salts, and transition metal complexes have all been employed to effect C-H (and C-C) bond activation but the large scale use of many of these approaches is limited by the high cost of the reagents.[125,126]

Since this Chapter is concerned with selective amidation, it should be noted that direct amidation (or amination) of hydrocarbon compounds has received very little attention but, for comparison, some methods which have been used to achieve such a transformation are outlined below.

N-(1-Adamantyl)acetamide has been obtained in high yield by oxidising (using electrochemical means) a mixture of adamantane and acetonitrile.[127]

A range of N-(1-adamantyl)alkylamide derivatives can be prepared by reacting adamantane in the presence of a nitrile with aluminium chloride in dichloromethane.[128]

Alkane compounds which contain one tertiary C-H bond can be converted to the corresponding acetamide derivative by irradiating a mixture which contains the substrate, heteropolytungstic acid, and acetonitrile. (Scheme 3.3)[129]

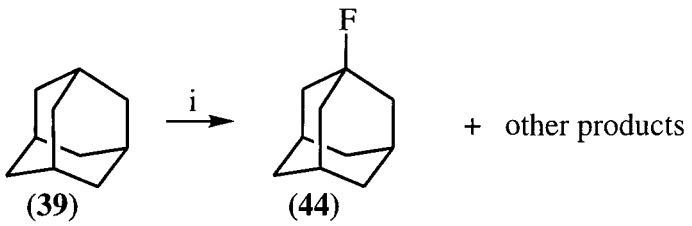
$$R_3C\text{-}H + CH_3CN \xrightarrow[H_3(PW_{12}O_{40}).6H_2O]{h\nu} R_3C\text{-}NHCOCH_3 + H_2$$

Scheme 3.3

In conclusion, only very limited attempts have been made to develop procedures for the direct amidation of hydrocarbon compounds and the methodology which has been developed is not generally applicable.

3.1.2 Selective amidation of adamantane using Selectfluor^{TM}

In Chapter 2 we established that the fluorination of various hydrocarbon compounds can be achieved using Selectfluor^{TM} as the fluorinating agent and the fluorination of adamantane **(39)** was performed as shown. (Scheme 3.4)

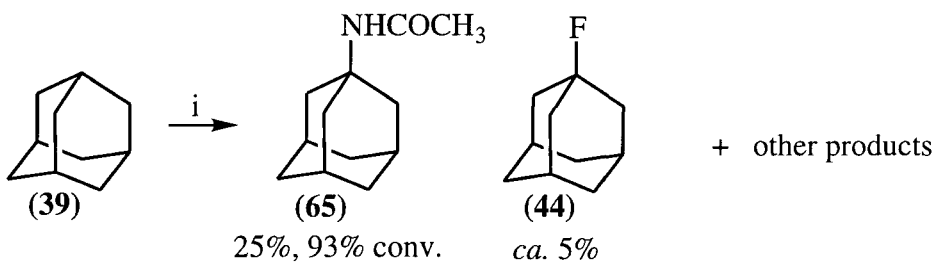


i = 1.8 Selectfluor^{TM}, CH_3CN, 82°C, 3 h.

Scheme 3.4

Given the result of this experiment, we reasoned that it may be possible to prepare difluoroadamantane using Selectfluor^{TM} and, therefore, the above reaction was repeated using a larger excess of Selectfluor^{TM} and a longer reaction time.

The resulting reaction mixture was worked up as usual and then purified by column chromatography on silica gel using 1:1 dichloromethane-methanol as the eluent to give N-(1-adamantyl)acetamide **(65)** (25%, 93% conv.) (Scheme 3.5).

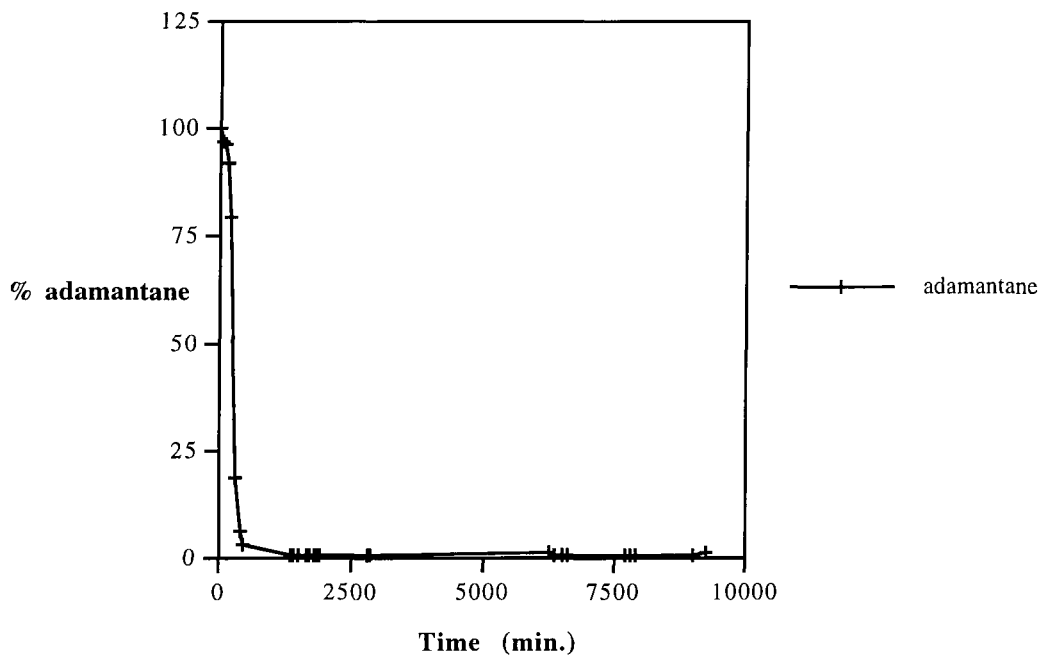


i = 2.5 Selectfluor^{TM}, CH_3CN, 82°C, 4.5 d.

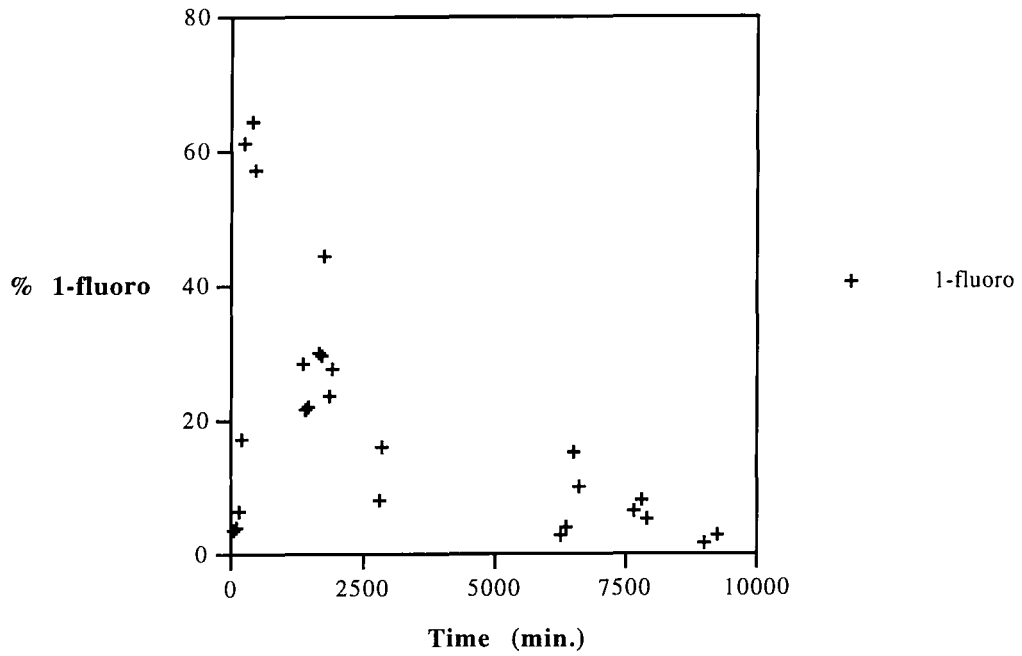
Scheme 3.5

The pure product was identified using NMR and IR spectrscopies, mass spectrometry, elemental analysis, melting point determination, and by comparison with literature reported data (references are given in the experimental section of this Chapter).

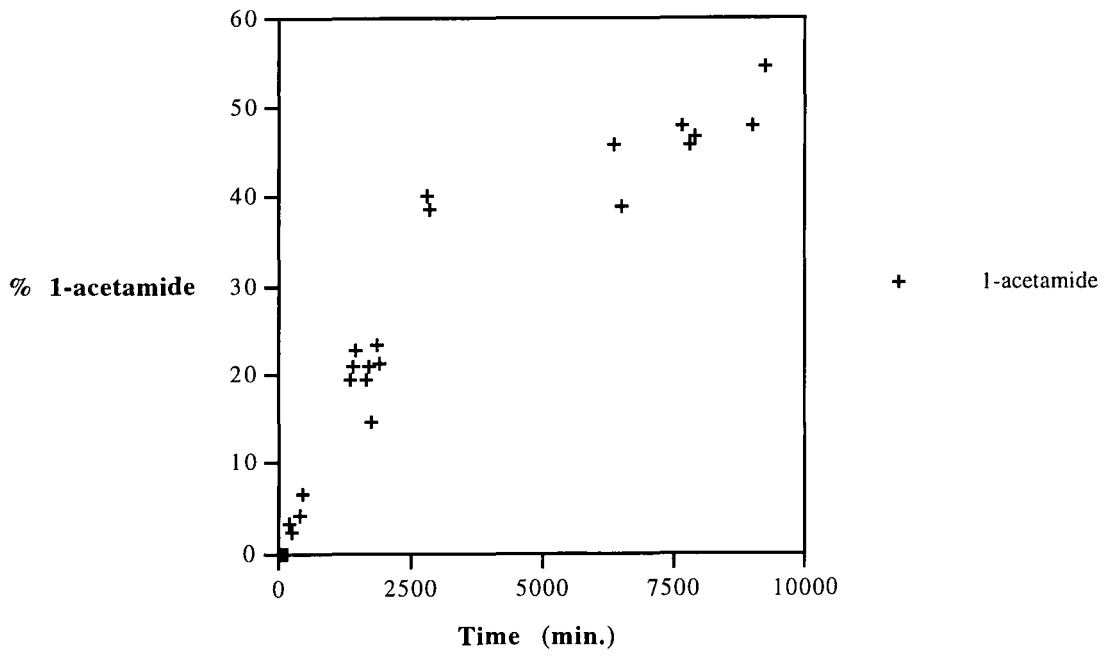
The result is very surprising and it suggests that 1-fluoroadamantane, which is the major product after 3 hours of reaction, is converted to N-(1-adamantyl)acetamide upon prolonged contact with Selectfluor^{TM}. To gain evidence which supports this postulation, the reaction was repeated and sampled at regular intervals. Each sample which was withdrawn from the reaction vessel was subject to GC analysis (after work-up) and the percentage area of adamantane **(39)**, 1-fluoroadamantane **(44)** (1-fluoro) and N-(1-adamantyl)acetamide **(65)** (1-acetamide) in each fraction was calculated and is plotted in Graphs 3.1, 3.2, and 3.3 respectively.



Graph 3.1



Graph 3.2



Graph 3.3

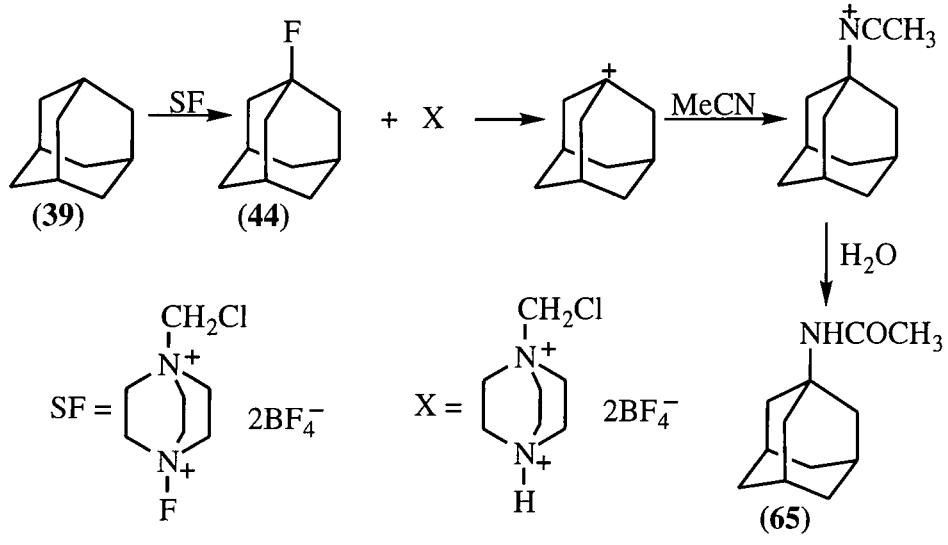
The most important information from the graphs is as follows:

- The amount of adamantane (**39**) in the reaction mixture decreased to *ca.* 1 area % in the first 1300 minutes of the reaction and remained at this value until the reaction was terminated.
- At a reaction time of 390 minutes the amount of 1-fluoroadamantane (**44**) in the reaction mixture was at its maximum value (*ca.* 64 area %). After this time, the amount of 1-fluoroadamantane (**44**) decreased as reaction time increased.
- The reaction mixture did not contain N-(1-adamantyl)acetamide (**65**) until 200 minutes from the start of the reaction but, after this point, the amount of acetamide (**65**) increased as reaction time increased.

If Graph 3.1 is compared with Graph 3.3 then it can be seen that N-(1-adamantyl)acetamide (**65**) was not produced from adamantane (**39**) and it is likely that the amide (**65**) was formed from 1-fluoroadamantane (**44**) for the following reasons, which are:

- N-(1-Adamantyl)acetamide (**65**) was first observed in the reaction mixture at a later reaction time than 1-fluoroadamantane (**44**) .
- The rate of formation of amide (**65**) is approximately equal to the rate at which fluoroadamantane (**44**) disappeared.
- At a reaction time of 390 minutes, the reaction mixture (reaction mixture A) contained adamantane (**39**) (6 area %), 1-fluoroadamantane (**44**) (64 area %), N-(1-adamantyl)acetamide (**65**) (4 area %), and many other products which could not be identified (26 area %). However, at a reaction time of 9230 minutes the reaction mixture (reaction mixture B) contained adamantane (**39**) (1 area %), 1-fluoroadamantane (**44**) (2 area %), N-(1-adamantyl)acetamide (**65**) (48 area %), and many other products which could not be identified (50 area %). In reaction mixture A the total amount of starting material and products which could not be identified is 32 area % and it is not possible to produce reaction mixture B, which contained the amide (**65**) in 48 area %, unless some monofluorinated adamantane was converted to the acetamide (**65**).

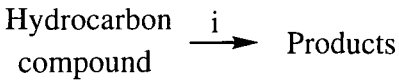
In conclusion, it is believed that 1-fluoroadamantane (**44**) was converted to N-(1-adamantyl)acetamide (**65**) and a possible mechanism for this transformation is shown (Scheme 3.6).



Scheme 3.6

Adamantane (**39**) is fluorinated (as described in Section 2.4.4; page 56) and this results in a reaction mixture which contains an N-protonated DABCO derivative. However, it is highly likely that the DABCO derivative is a very weak base and consequently a strong acid. This means that the reaction mixture is highly acidic and it promotes ionisation of 1-fluoroadamantane to give 1-adamantyl cation. The cation reacts with acetonitrile to give, after an aqueous work-up, the observed amide (**65**) and this sequence constitutes a Ritter-type reaction.[113]

In principle, it may be possible to avoid the transformation of fluorinated adamantane to N-(1-adamantyl)acetamide (**65**) by employing a reaction solvent which is relatively non-nucleophilic. Consequently, the fluorination of adamantane (**39**) (or decalin (**46**)) was attempted in a range of non-nucleophilic solvents as shown (Scheme 3.7) and gave, after the usual work-up, a product which was analysed (^{19}F NMR and GC-MS). The results are shown in Table 3.1.



i = Selectfluor^{TM}, solvent, heat, 24 h.

Scheme 3.7

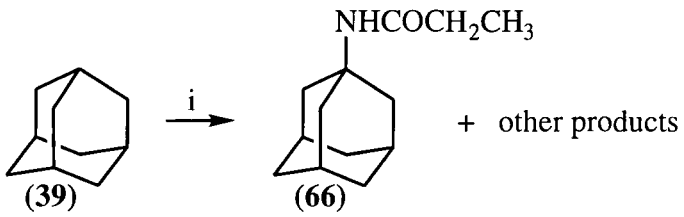
Substrate	Solvent	Reaction Temperature °C	Major Products
adamantane (**39**)	dichloromethane	45	adamantane (**39**) recovered
adamantane (**39**)	dichloromethane-trifluoroacetic acid (6% (v/v))	45	adamantane (**39**) recovered
adamantane (**39**)	nitromethane	82	N-(adamantyl) propylamide (**66**)
decalin (**46**) (4 h)	nitroethane	82	decalin (**46**) recovered
decalin (**46**) (48 h)	nitroethane	82	decalin (**46**) recovered

Table 3.1

Both dichloromethane and dichloromethane-trifluoroacetic acid do not facilitate the fluorination of adamantane using Selectfluor^{TM}.

It is interesting to note that the major product obtained from the nitromethane reaction was N-(1-adamantyl)propylamide (**66**) (identified using GC-MS only) and, this result is surprising. However, commercial nitromethane contains a small amount of propionitrile[123] and, therefore, it is likely that adamantane (**39**) was converted to N-(adamantyl)propylamide (**66**) in an analogous fashion to the conversion of adamantane (**39**) to N-(1-adamantyl)acetamide (**65**).

To confirm this hypothesis, adamantane (**39**) was reacted with Selectfluor^{TM} in propionitrile as shown (Scheme 3.8) and, as expected, this reaction gave (after purification of the crude product by column chromatography on silica gel using chloroform as the eluent), N-(1-adamantyl)propylamide (**66**) (65%, 100% conv.).



65%, 100% conv.

i = Selectfluor^{TM}, CH_3CH_2CN, 82°C, 3 d.

Scheme 3.8

The product was characterised using standard techniques and the ^{13}C NMR spectrum of the product was assigned by comparison with the NMR spectrum of N-(1-adamantyl)acetamide (**65**).

In contrast to nitromethane, commercial nitroethane does not contain propionitrile[123] and, therefore, nitroethane was explored as a fluorination solvent. Table 3.1 shows that only starting material was obtained from this reaction and this suggests that the propionitrile in nitromethane facilitates fluorination of adamantane but without this 'impurity' in nitroethane reaction does not occur.

3.2 Conclusions

It has been shown that difluorination of the model hydrocarbon compounds is not possible using Selectfluor^{TM} because an acidic reaction medium results upon monofluorination of the substrate.

It was reasoned that such a transformation may be inhibited by the use of a relatively non-nucleophilic reaction solvent but, unfortunately, all of the non-nucleophilic solvents which were investigated do not facilitate fluorination.

The use of Selectfluor^{TM} for the preparation of amidated compounds is not economical and, consequently, this area of work was not pursued further.

3.3 Amidation using elemental fluorine

The next part of this Chapter details an investigation into the use of a combination of elemental fluorine and boron trifluoride (or tetrafluoroboric acid) for the preparation of selectively functionalised hydrocarbon compounds.

In the previous section we observed that Selectfluor^{TM} can be used to prepare selectively amidated hydrocarbon compounds and that the key to this transformation was the acidic reaction mixture which results upon fluorination of the substrate. This

led us to reason that it may be possible to perform a similar transformation by passing elemental fluorine through an acidic mixture of the hydrocarbon substrate and acetonitrile. Our attempts to exemplify and extrapolate this idea will now be detailed.

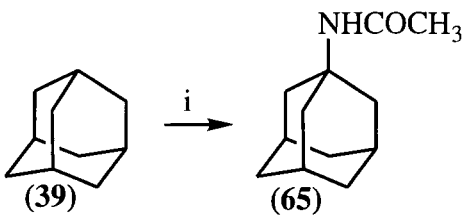
3.3.1 Preliminary investigation

We began by investigating the affect of both boron trifluoride and tetrafluoroboric acid on the direct fluorination of adamantane (Table 3.2). Reactions were carried out by passing elemental fluorine through a cooled (0°C), stirred mixture of adamantane, an acid and acetonitrile. The resulting reaction mixture was worked up and analysed (GC-MS) and the ratio of adamantane **(39)** (Ad) : 1-fluoroadamantane **(44)** (1-F-Ad) : N-(1-adamantyl)acetamide **(65)** (1-Ad-amide) obtained in each crude product is shown (Table 3.2). The corresponding ratio for the direct fluorination of adamantane has also been tabulated for comparison.

Row number	Additive	Ad (39): 1-F-Ad (44) : 1-Ad-amide (65)
1	-	1.0 : 2.6 : 0
2	HBF_4 (1 equiv.)	1.0 : 0 : 1.6
3	HBF_4 (0.1 equiv.)	6.4 : 5.1 : 1.0
4	BF_3 (1 equiv.)	1.0 : 0 : 1.6
5	BF_3 (0.1 equiv.)	2.2 : 4.5 : 1.0

Table 3.2

The crude product displayed in row 4 was purified by column chromatography on silica gel using 1:1 dichloromethane-methanol as the eluent and gave adamantane **(39)** (26%) which eluted prior to N-(1-adamantyl)acetamide **(65)** (54%, 74% conv.) (Scheme 3.9).



54%, 74% conv.

i = 4 equiv. 10% F_2/N_2, $BF_3.Et_2O$, CH_3CN, 0°C.

Scheme 3.9

The results contained within rows 2 and 4 of Table 3.2 show that one equivalent of acid promotes the complete conversion of 1-fluoroadamantane (**44**) to the corresponding acetamide (**65**). In contrast, using a catalytic amount of acid gave a crude product mixture which contained a relatively large amount of fluorinated adamantane (rows 3 and 5 of Table 3.2). It is likely that the acid concentration in these latter reactions is insufficient to facilitate the complete conversion of fluoroadamantane (**44**) to N-(1-adamantyl)acetamide (**65**).

It is interesting to note that the reaction mixtures which were prepared using boron trifluoride were very similar to those which were prepared using the corresponding amount of tetrafluoroboric acid.

Table 3.2 shows that the addition of boron trifluoride or tetrafluoroboric acid to the reaction mixture does not affect the fluorination step of the reaction but, instead, promotes transformation of the fluorinated product.

3.3.2 Selective amidation of other hydrocarbon compounds

The preliminary study highlighted that adamantane can be selectively amidated using elemental fluorine and, therefore, we performed the amidation of other hydrocarbon compounds to ascertain the scope of the reaction.

All reactions were carried out under the same conditions as the preliminary study. (Scheme 3.10) After addition of all the fluorine, a small sample of the reaction mixture was withdrawn from the reaction vessel, added to potassium fluoride to remove any hydrogen fluoride, filtered, and then analysed (^{19}F NMR) for fluoroalkane. If fluoroalkane was detected, the reaction mixture was heated for 15 minutes and after this time no fluoroalkane remained. The mixture was then worked up to give a crude product mixture which was purified by either recrystallisation or column chromatography. Pure products were characterised using standard techniques.

Table 3.3 shows a summary of the results obtained and the corresponding direct fluorination results (Chapter 2) have been included for comparison.

$$RH \xrightarrow{i} RNHCOCH_3$$

i = 10% F_2/N_2, $BF_3.Et_2O$, CH_3CN, 0°C.

Scheme 3.10

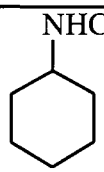
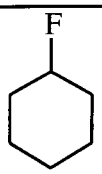
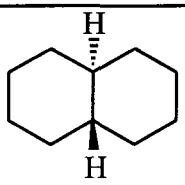
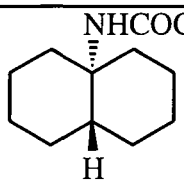
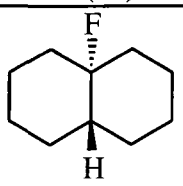
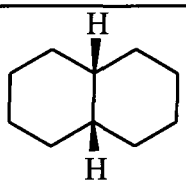
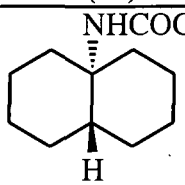
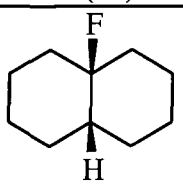
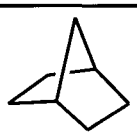
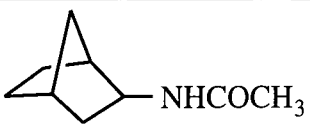
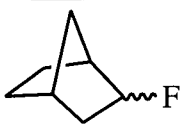
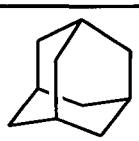
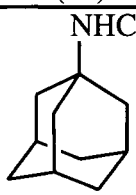
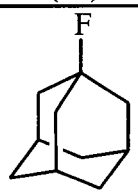
Substrate	Amidated Product(s) Yield (Conv.)[a] %	Fluorinated Product(s) Yield (Conv.)[b] %
 **(36)**	 **(67)** 51 (53)	 **(37)** 63 (53)
 **(48)**	 **(68)** 45 (49)	 **(49)** 54 (68)
 **(46)**	 **(68)** 49 (67)	 **(47)** 57 (64)
 **(41)**	 **(69)** 45 (60)	 **(43A, B)** 41 (60)
 **(39)**	 **(65)** 54 (74)	 **(44)** 65 (70)

Table 3.3

[a] Corresponds to pure isolated products.

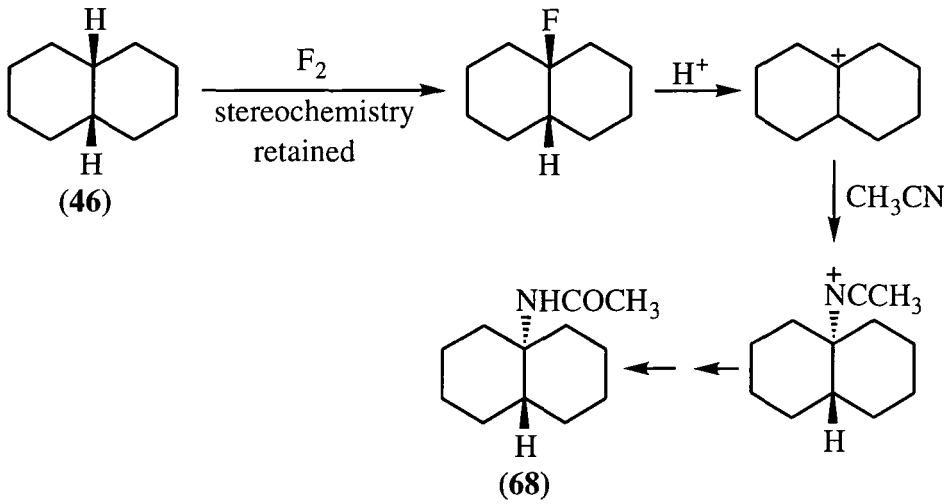
[b] After work-up.

N-(Cyclohexyl)acetamide (67) - The crude product from this reaction was distilled to remove cyclohexane **(36)** (47%) and the remaining residue was recrystallised from acetonitrile to give pure N-(cyclohexyl)acetamide **(67)** (51%, 53% conv.).

N-(*trans*-9-Decalyl)acetamide (68) from *cis*-decalin (46) - Distillation and recrystallisation (as for the cyclohexane reaction) gave *cis*-decalin **(46)** (33%) and N-(*trans*-9-decalyl)acetamide **(68)** (49%, 67% conv).

N-(*trans*-9-Decalyl)acetamide (68) from *trans*-decalin (48) - The procedure as for *cis*-decalin was followed and gave *trans*-decalin **(48)** (51%) and N-(*trans*-9-decalyl)acetamide **(68)** (45%, 49% conv).

Both *cis*- and *trans*-decalin **(46, 48)** gave the *trans*-acetamide **(68)** and this observation supports the proposed mechanism which is illustrated using *cis*-decalin **(46)** (Scheme 3.11).



Scheme 3.11

Decalin is fluorinated with retention of configuration (Section 2.4.1; page 50) and then ionised by BF_3/HBF_4 to give 9-decalyl cation. Reaction of the cation with acetonitrile gives the *trans*-amide **(68)** which is more thermodynamically stable than the *cis*-isomer.

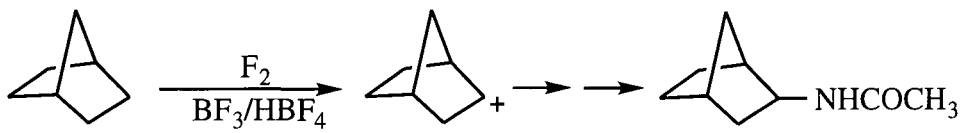
N-(*exo*-2-norbornyl)acetamide (69) - Purification by recrystallisation from acetonitrile gave N-(*exo*-2-norbornyl)acetamide **(69)** (45% 60% conv.).

A HETCOR NMR spectrum was used to ascertain that amidation of norbornane had not occurred at the tertiary C-H bond of norbornane and the ^{13}C and ^{1}H NMR spectra of the product both match the corresponding spectra which have been reported[130] for N-(*exo*-2-norbornyl)acetamide **(69)**.

Direct fluorination of norbornane (**41**) (Section 2.4.1; page 50) gives an isomeric mixture of *exo*- and *endo*-2-fluoronorbornane (**43A, B**) in the ratio of 5 : 1 respectively but amidation of the substrate gives only the *exo*-amide (**69**). There are two possible explanations for the difference between these results, which are:

1) The amidation reaction gave both *exo*- and *endo*-acetamide in the ratio of 5 : 1 but the *endo*-acetamide, the minor compound, was separated from the major product during recrystallisation.

2) It is likely that the amidation of norbornane proceeds through the carbocation intermediate which is shown (Scheme 3.12).



(**41**) (**69**)

Scheme 3.12

Acetonitrile can react with 2-norbornyl cation to give both *exo*- and *endo*-acetamide products but it is likely that formation of the *exo*-isomer, which is more thermodynamically stable than the *endo*-isomer, occurs preferentially.

3.3.3 Summary of amidation reactions

Table 3.3 shows that fluorination yields are, in general, slightly higher than the corresponding amide yield but fluoroalkane yields correspond to the amount of product which was present in the crude product mixture, whereas, amide yields correspond to pure isolated products. It is inevitable that some amide was lost during purification and, therefore, it is likely that the yield of amide in the crude product was equal to (or even greater than) the yield of the corresponding fluorinated product.

All amidation reactions proceed with excellent regioselectivity which is determined by the fluorination step of the reaction. However, amidated products do not necessarily have the same stereochemistry as the corresponding fluorinated product and this supports the suggestion that the fluoroalkane is ionised to give a carbocationic intermediate which is then attacked by acetonitrile.

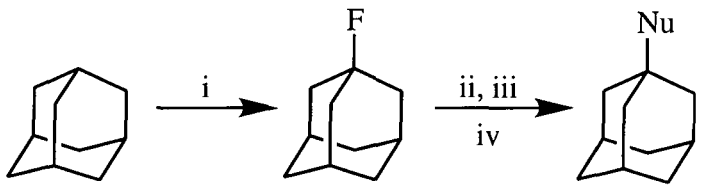
3.4 Functionalisation of adamantane

In principle, the selective functionalisation of hydrocarbon compounds could be accomplished by employing the experimental procedure which is described above and a reaction solvent which is relatively nucleophilic.

However, we established previously that the selective fluorination of hydrocarbon compounds could not been achieved in a solvent other than a nitrile. Therefore, replacing acetonitrile either wholly or partly with another fluorination solvent is likely to compromise the selectivity of the methodology. Also, other problems can be envisaged if acetonitrile is replaced by another nucleophile, which include:

- Elemental fluorine may react preferentially with the nucleophile and not the hydrocarbon substrate.
- Boron trifluoride may co-ordinate to the nucleophile prior to the addition of fluorine to the reaction mixture.
- The nucleophile may not be compatible with elemental fluorine.

The experimental protocol shown (Scheme 3.13) was devised to avoid these problems and then used to selectively functionalise a model hydrocarbon compound (adamantane **(39)**).



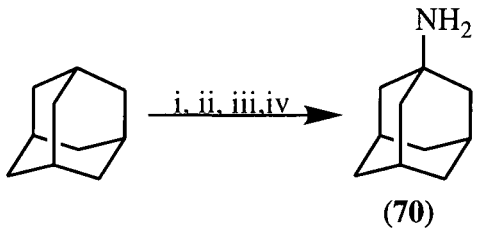
i = 10% F_2/N_2, CH_3CN, 0°C.
ii = extract using DCM, wash (H_2O), dry ($MgSO_4$).
iii = $BF_3.Et_2O$, 1-2 min.
iv = NuH.

Scheme 3.13

Fluorination of adamantane **(39)** was performed as detailed previously (Chapter 2) and, after addition of all the fluorine, the reaction mixture was poured into water and extracted using dichloromethane. The combined organic extracts were washed multiple times with copious amounts of water to remove any residual acetonitrile. An excess of boron trifluoride etherate was then added to the organic extract which was dried and reduced (to a volume of *ca.* 50 cm^3) and after 1-2 minutes an excess of the nucleophile was added to this mixture.

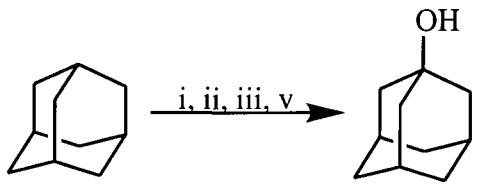
1-Aminoadamantane **(70)**, 1-hydroxyadamantane **(71)**, and 1-ethoxyadamantane **(72)** have been prepared in good yield using this procedure (Scheme 3.14). 1-Hydroxy- and 1-ethoxyadamantane **(71, 72)** were both purified by column chromatography on silica gel using 1:1 diethyl ether-hexane and dichloromethane respectively as the eluent. 1-Aminoadamantane **(70)** was isolated using recrystallisation and all three products were characterised using standard techniques.

In all cases, 1-fluoroadamantane (**44**) (^{19}F NMR) was not present in the crude product mixture and, therefore, the conversion of the reaction was assumed to be equal to the conversion of adamantane (**39**) to 1-fluoroadamantane (**44**) (Chapter 2). It was very difficult to remove all of the acetonitrile from the fluorinated reaction mixture and, frequently, a large amount of N-(1-adamantyl)acetamide was obtained in the crude product mixture. However, with perseverance all acetonitrile can be removed from the fluorinated reaction mixture and the product mixtures which were eventually purified (Scheme 3.14) did not contain any acetamide.



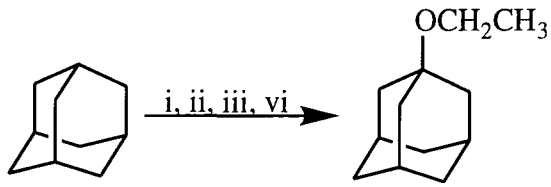
(70)

51%, 70% conv.



(71)

66%, 70% conv.



(72)

62%, 70% conv.

i = 10% F_2/N_2, CH_3CN, 0°C.
ii = extract using DCM, wash (H_2O), dry ($MgSO_4$).
iii = $BF_3.Et_2O$, 1-2 min.
iv = $NH_{3(aq)}$
v = H_2O
vi = CH_3CH_2OH

Scheme 3.14

3.5 Conclusions

Difluorination of adamantane using Selectfluor^{TM} was attempted but, surprisingly, gave N-(1-adamantyl)acetamide (**65**) as the major product. This transformation is highly disadvantageous and constitutes a serious limitation of the Selectfluor^{TM} reagent.

Following this observation, a range of selectively amidated hydrocarbon compounds were prepared by passing elemental fluorine through a mixture of the hydrocarbon compound, acetonitrile, and tetrafluoroboric acid/boron trifluoride. Amides were obtained in reasonable yield and with excellent regioselectivity and it is likely that this methodology could be applicable to a wide range of hydrocarbon compounds.

Selective functionalisation of adamantane was achieved by performing the preparation and ionisation of fluoroadamantane in separate steps and, in principle, this methodology could be extended to involve a range of hydrocarbon compounds and a range of nucleophiles.

In conclusion, methodology for the selective functionalisation of alkane compounds has been developed and exemplified and this illustrates the use of elemental fluorine for the preparation of compounds which do not contain fluorine.

Chapter 4: Fluorination of Hydrocarbon Derivatives

4.1 Introduction

In Chapter 2 the selective fluorination of some hydrocarbon compounds was performed and, in general, fluorination occurred at the most electron rich carbon-hydrogen bond(s) in the substrate molecule. Given this result, we postulated that if an electron withdrawing group (EWG) was attached to an alkyl chain it would reduce the electron density of the adjacent C-H bonds and, consequently, fluorination of these sites would be disfavoured. This led us to reason that it may be possible to direct fluorination to particular sites of an alkyl chain by attaching functionality to strategic positions of the chain. Consequently, we have investigated the selective fluorination of alkyl chains which are attached to an electron withdrawing group.

4.2 Approach

We selected a range of substrates which are available commercially and have either an ester group or a halide atom attached to an alkyl chain. Fluorination of all substrates was attempted using both elemental fluorine and Selectfluor^{TM} and these reactions will be discussed separately in the following text and then compared at the end of each section.

4.3 Fluorination of ester derivatives

4.3.1 Fluorination of methyl valerate (73) using elemental fluorine

Fluorination of methyl valerate **(73)** was performed by passing excess elemental fluorine, as a 10% mixture with nitrogen, through a cooled (0°C), stirred solution containing methyl valerate and acetonitrile. The crude product mixture, which was obtained after work-up, contained methyl 3- and 4-fluorovalerate **(74A, B)** (21%, 66% conv.)* in the ratio of 1.0 : 3.2 respectively, small amounts of other monofluorinated methyl valerate isomers, other products (>27) which could not be identified and tar (7%).

Preparative scale GC was used to isolate a sample of methyl 3- and 4-fluorovalerate **(74A, B)** as an isomeric mixture from the crude product and standard characterisation techniques were used to identify the two fluorinated products. (Scheme 4.1)

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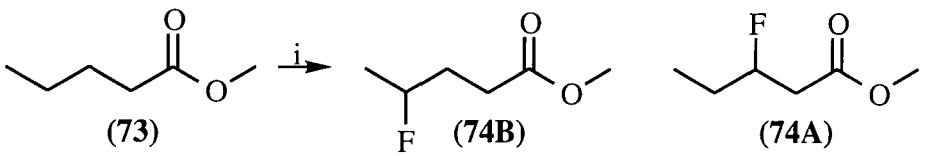
* Yield, conversion, and tar quantities were all calculated as described in Section 2.3.1 (page 44) and the ratio of fluorinated products was determined using ^{19}F NMR spectroscopy.



(73) (74B) (74A)

product ratio = 3.2 : 1.0 respectively

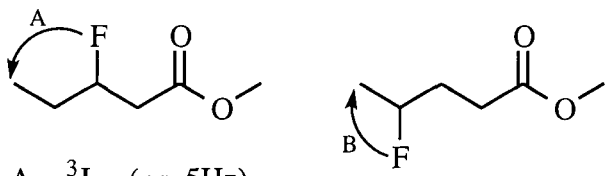
21%, 66% conv.

i = 5 equiv. 10 $\%F_2/N_2$, CH_3CN, 0°C.

Scheme 4.1

The ^{13}C NMR spectrum of the pure isomeric mixture was used to determine the identity of the isomers. The ^{13}C NMR spectrum contains two peaks at δ_C= *ca.* 90 ppm which both display a coupling constant of *ca.* 180Hz and these data indicate the presence of two CHF carbon atoms.

The key to the exact identity of the major isomer was the observation that the methyl carbon signal displays a two bond C-F coupling constant (*ca.* 20Hz). In contrast, the methyl carbon signal of the minor product displays a three bond coupling constant (*ca.* 5Hz) which is much smaller. (Scheme 4.2)



A = $^3J_{CF}$ (*ca.* 5Hz)

B = $^2J_{CF}$ (*ca.* 20Hz)

Scheme 4.2

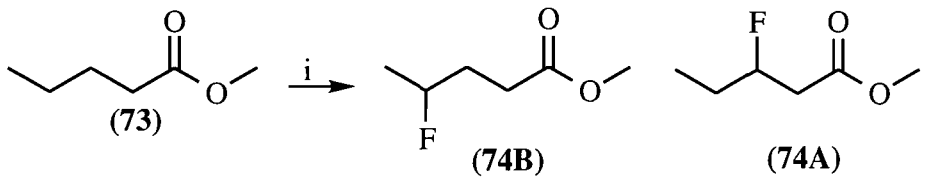
The product distribution can be explained by considering the negative inductive effect of the ester group. The electron density of the C-4 C-H bonds is greater than the C-3 because C-4 is further from the electron withdrawing centre and, consequently, fluorination (which is an electrophilic process) occurs more readily at C-4.

It is interesting to note that only a small amount of methyl 5-fluorovalerate was obtained and this suggests that the primary C-H bonds (which are furthest removed from the ester group) have a lower electron density than both the C-3 and C-4 C-H bonds which are closer to the functionality.

The yield of methyl 3- and 4-fluorovalerate (**74A, B**) is low and a large amount of by-products (which could not be identified) and tar were also obtained. This indicates that the direct electrophilic fluorination of methyl valerate (**73**) proceeds with poor selectivity and it is likely that this results because the substrate is highly electron depleted.

4.3.2 Fluorination of methyl valerate (73) using Selectfluor^{TM}

Fluorination of methyl valerate (**73**) was also carried out using Selectfluor^{TM} as shown (Scheme 4.3). The crude product mixture which was obtained after work-up contained methyl 3-fluorovalerate (**74A**) and methyl 4-fluorovalerate (**74B**) (64%, 45% conv.) in the ratio of 1.0 : 1.2 respectively, a small amount of other fluorinated methyl valerates (<5%) and products (>10) which could not be identified.



product ratio = 1.2 : 1.0 respectively
64%, 45% conv.

i = 1.1 Selectfluor^{TM}, CH_3CN, 82°C, 16 h.

Scheme 4.3

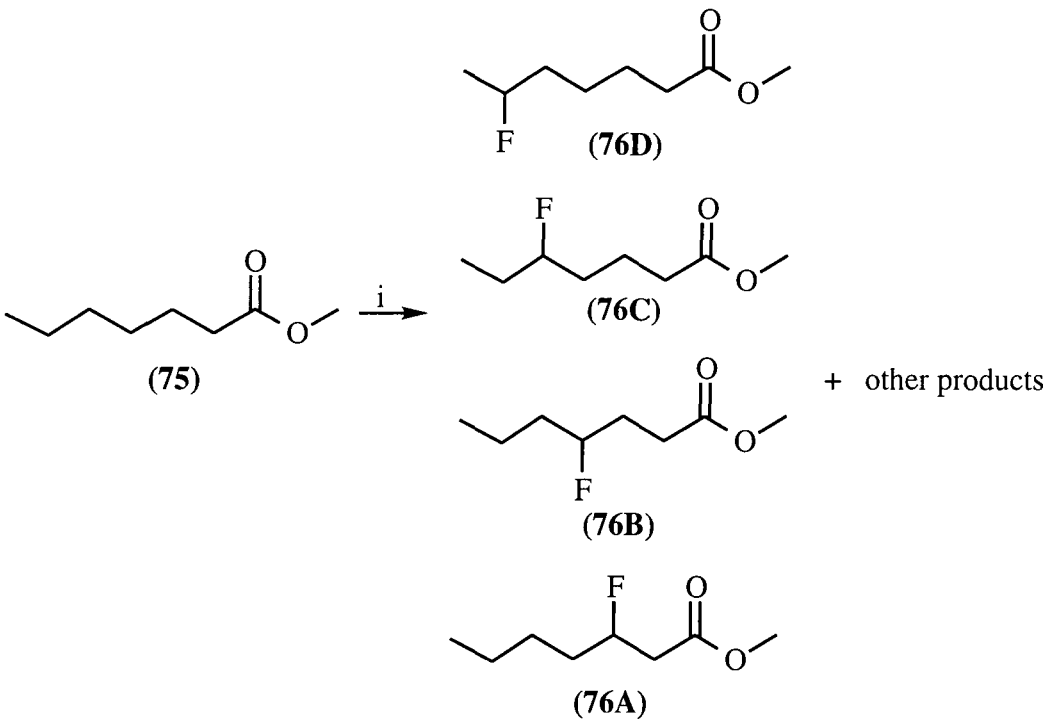
The main products from this reaction have the same ^{19}F NMR chemical shift values, mass spectra and retention times as the products which were isolated previously from the direct fluorination of methyl valerate. Therefore, the major products from this reaction were not isolated

The crude product contained fewer by-products than the corresponding crude product which was prepared using elemental fluorine but a large amount of starting material remained after 16 hours of heating the reaction mixture. This suggests that the substrate is relatively deactivated with respect to fluorination using Selectfluor^{TM}.

The ester group exhibits a negative inductive effect and this influence is stronger at C-3 relative to C-4. Consequently, it is surprising that there was an approximately equal amount of methyl 3-fluorovalerate and methyl 4-fluorovalerate in the crude product mixture.

4.3.3 Fluorination of methyl enanthate (75) using Selectfluor™

Fluorination of methyl enanthate (**75**) using Selectfluor™ was carried out as for the fluorination of methyl valerate (**73**) and gave a crude product mixture which contained methyl 3-, 4-, 5-, and 6-fluoroenanthate (**76A-D**) (48%, 57% conv.) in the ratio of 1.0 : 1.3 : 1.3 : 3.7 respectively, a trace amount of other fluorinated methyl enanthates, methyl enanthate acetamide (4 area %) and products (>10) which could not be identified. (Scheme 4.4)



product ratio = 3.7 : 1.3 : 1.3 : 1.0 respectively
48%, 57% conv.

i = 1.1 Selectfluor™, CH_3CN, 82°C, 16 h.

Scheme 4.4

Preparative scale GC was used to isolate a pure isomeric mixture of the four major fluorinated methyl enanthate isomers which were present in the crude product. The identity of the major isomer was then determined using standard 1-D and 2-D NMR experiments and was found to be methyl 6-fluoroenanthate (**76D**). The key to the assignment was the observation that the CH_3 unit of the alkyl chain displayed a two bond CF coupling constant in the ^{13}C NMR spectrum of the product mixture.

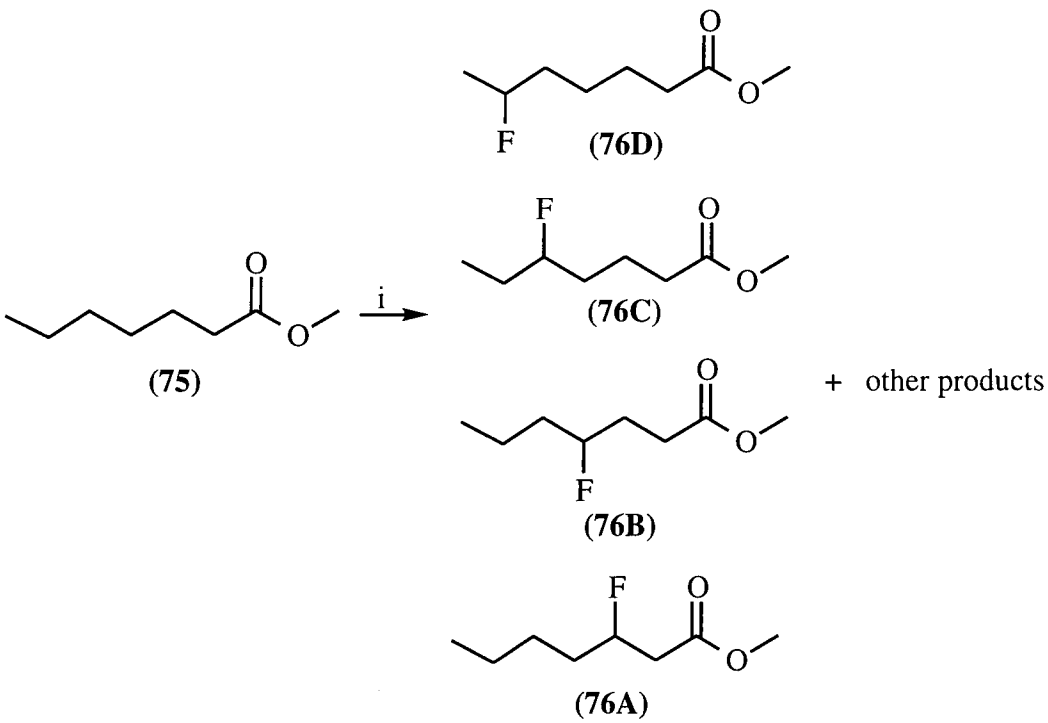
Unfortunately, it was only possible to identify the exact structure of the major isomer in the product mixture, the other three isomers could not be identified exactly

as there is an insufficient difference in the relative amount of these isomers to facilitate interpretation of ^{13}C NMR spectrum.

The identity of the three most minor isomers was postulated by considering the relative ratio of fluorinated methyl valerate isomers which was obtained upon fluorination of methyl valerate.

4.3.4 Fluorination of methyl enanthate (75) using elemental fluorine

The direct fluorination of methyl enanthate (**75**) was carried out in an analogous fashion to the direct fluorination of methyl valerate and gave a crude product mixture which contained the products shown in Scheme 4.5, a trace amount of methyl 7-fluoroenanthate and products (>20) which could not be identified.



product ratio = 5.6 : 6.4 : 3.5 : 1.0 respectively

68%, 64% conv.

i = 3 equiv. 10% F_2/N_2, CH_3CN, 0°C.

Scheme 4.5

^{19}F NMR and GC-MS data of the crude product were used to identify the four major products.

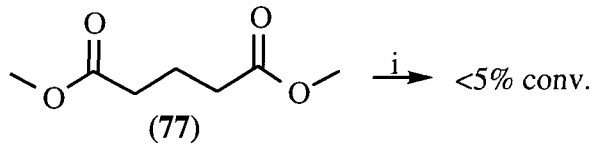
Fluorination at C-5 and C-6 of methyl enanthate occurs at approximately the same rate and fluorination occurs preferentially at secondary sites that are furthest

from the electron withdrawing group. Therefore, it is probable that the product distribution is controlled by the inductive effect of the ester group.

4.3.5 Attempted fluorination of dimethyl glutarate (77)

Fluorination of dimethyl glutarate (**77**) was attempted using both elemental fluorine and Selectfluor^{TM} (Scheme 4.6 and 4.7 respectively) but, in both cases, only a small amount of fluorinated diester was observed.

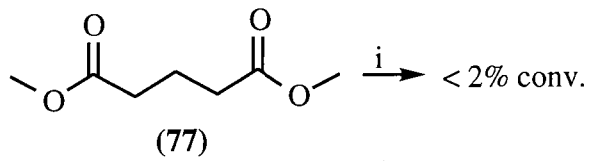
These results suggest that the secondary C-H bonds of this substrate do not have sufficient electron density to facilitate fluorination.



(77)

i = 3.5 equiv. 10% F_2/N_2, CH_3CN, 0°C.

Scheme 4.6



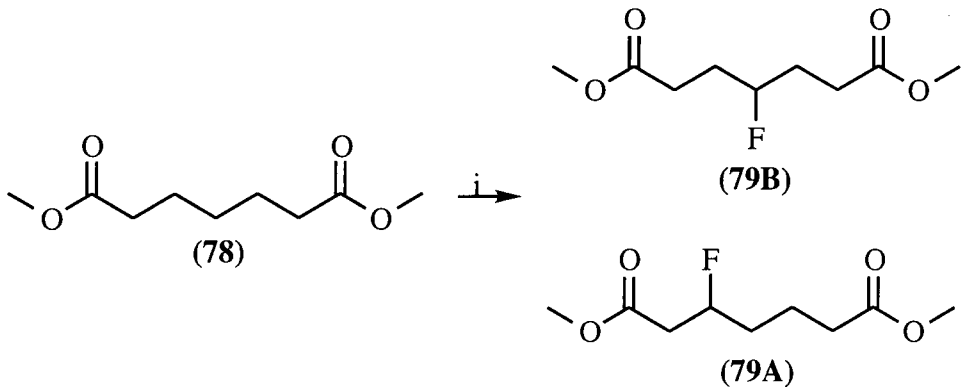
(77)

i = 1.1 Selectfluor^{TM}, CH_3CN, 82°C, 7 d.

Scheme 4.7

4.3.6 Fluorination of dimethyl pimelate (78) using elemental fluorine

The direct fluorination of dimethyl pimelate (**78**) was performed using the usual procedure and gave a crude product mixture which contained dimethyl 3- and 4-fluoropimelate (**79A, B**) (54%, 98% conv.) in the ratio of 1.0 : 1.7 respectively, and other products (>20) which could not be identified. Purification of the crude product by column chromatography on silica gel using 4:1 petroleum ether-ethyl acetate as the eluent gave dimethyl 3- and 4-fluoropimelate (**79A, B**) as an isomeric mixture. (Scheme 4.8)



product ratio = 1.7 : 1.0 respectively

57%, 98% conv.

i = 7 equiv. 10% F_2/N_2, CH_3CN, 0°C.

Scheme 4.8

The identity of the isomeric mixture was determined using standard 1-D and 2-D NMR experiments and, as expected from the above results, the major isomer was identified as dimethyl 4-fluoropimelate (**79B**).

4.3.7 Attempted fluorination of dimethyl pimelate (78) using Selectfluor^{TM}

Fluorination of dimethyl pimelate using Selectfluor^{TM} was attempted by heating (82°C) a mixture which contained the diester (**78**), a small excess of Selectfluor^{TM}, and acetonitrile for 16 hours but only a small amount (<10% conv.) of reaction was observed after this time.

4.3.8 Summary of results

A summary of the relative ratios of attack at each C-H bond in each of the substrates which are discussed above is shown (Table 4.1).

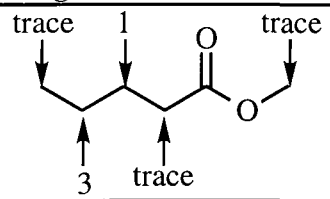
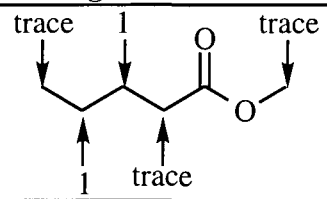
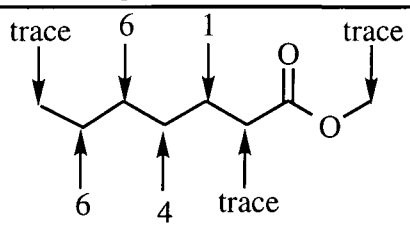
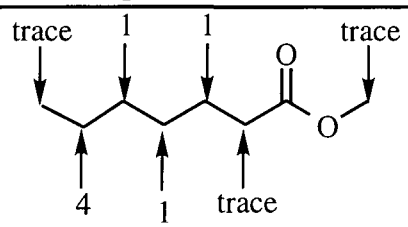
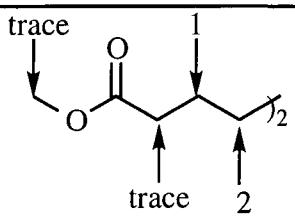
Substrate	Relative Selectivities at each Position using Elemental Fluorine	Relative Selectivities at each Position using Selectfluor™
Methyl valerate (73)		
Methyl enanthate (75)		
Dimethyl glutarate (77)	<5% conv.	<2% conv.
Dimethyl pimelate (78)		<10% conv.

Table 4.1

Table 4.1 shows that fluorination of the alkyl chain which is attached to a methyl ester is not affected significantly by the electron withdrawing group with the exception that only a trace amount of fluorination occurs at the secondary C-H bonds which are adjacent to the ester group.

However, in most cases fluorination occurs preferentially at secondary sites that are furthest from the ester group. When elemental fluorine is employed as the fluorinating agent, fluorination at sites that are greater than three bond lengths away from the EWG group is not influenced by it, whereas, when Selectfluor™ is

employed as the fluorinating agent, the functional group does not influence the fluorination of sites that are greater than four bond lengths away from it.

Fluorination of dimethyl glutarate (**77**) was not possible using either Selectfluor^{TM} or elemental fluorine and this suggests that the substrate is strongly deactivated. However, reaction of elemental fluorine with dimethyl pimelate (**78**) gave fluorinated products in excellent conversion and this demonstrates that increasing the distance between the ester groups results in a more reactive substrate.

Dimethyl pimelate (**78**) could not be fluorinated using Selectfluor^{TM} and this shows that elemental fluorine is a more powerful fluorinating agent than Selectfluor^{TM}.

In conclusion, secondary C-H bonds which are adjacent to a methyl ester are highly deactivated to fluorination using both elemental fluorine and Selectfluor^{TM}. However, a methyl ester does not have much affect on the fluorination of secondary C-H sites which are greater than one bond length away. Both fluorinating agents react with a given substrate to give a similar product distribution.

4.4 Fluorination of alkyl halides

4.4.1 Attempted fluorination of both 1-iodohexane (80) and 1-bromohexane (81)

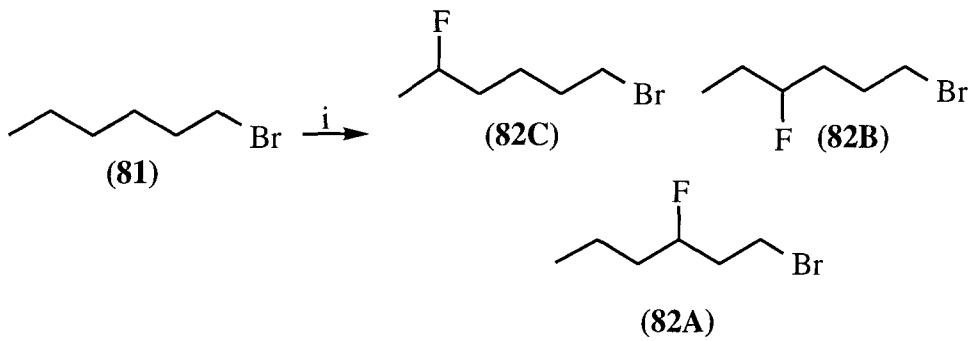
The direct fluorination of 1-iodohexane (**80**) was attempted using the usual procedure but, on addition of fluorine to the reaction mixture, the mixture changed instantly from colourless to purple and, after addition of all the fluorine, the reaction mixture was de-colourised using aqueous sodium metabisulfite and then subject to the usual work-up to give a crude product mixture.

Analysis (GC-MS and ^{19}F NMR) of the product mixture showed that it contained 1-iodohexane (**80**) (85 area %) and a large number (>20) compounds which do not contain fluorine and could not be identified.

Both the direct fluorination of 1-bromohexane (**81**) and the reaction of Selectfluor^{TM} with 1-iodohexane (**80**) gave a similar result to the reaction of elemental fluorine with 1-iodohexane (**80**). Therefore, it is suspected that the fluorinating agents, which are also oxidising agents, attack the halogen atom in each of these substrates.

4.4.2 Fluorination of 1-bromohexane (81) using Selectfluor™

Fluorination of 1-bromohexane (**81**) using Selectfluor™ was performed in the usual manner and gave the three isomers of bromofluorohexane (**82A-C**) which are shown in Scheme 4.9 and a small number of products which could not be identified.



product ratio = 3.8 : 1.9 : 1.0 respectively

75% yield, 30% conv.

i = 1.1 Selectfluor™, CH_3CN, 82°C, 16 h.

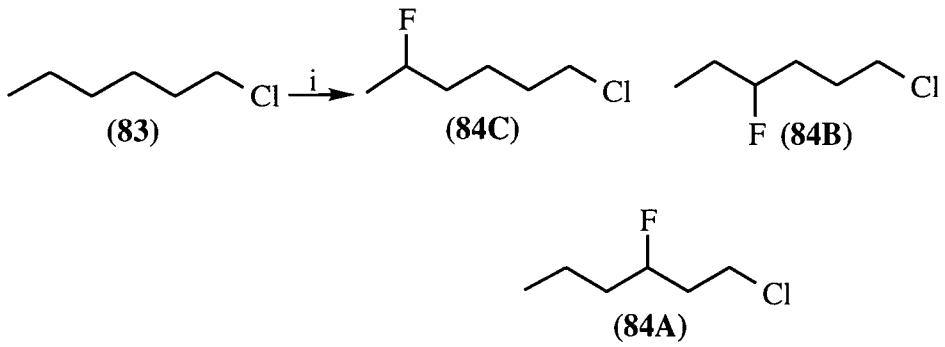
Scheme 4.9

The two most abundant products from this reaction were separated as an isomeric mixture from the crude product using preparative scale GC and the pure sample was characterised using standard techniques.

The major and minor products were identified as 1-bromo-5-fluorohexane (**82C**) and 1-bromo-4-fluorohexane (**82B**) respectively using the NMR spectra of the mixture. The key to the assignment was the observation that the major methyl carbon displays a 20Hz (i.e. two bond CF) and the minor a 5Hz (i.e. three bond CF) coupling constant. Based on the results in Section 4.3, it is postulated that the third fluorinated isomer in the crude product mixture is 1-bromo-3-fluorohexane (**82A**).

4.4.3 Fluorination of 1-chlorohexane (83) using Selectfluor™

Reaction of Selectfluor™ with 1-chlorohexane (as described for 1-bromohexane (**81**) gave a product mixture which contained 1-chloro-3-, 4-, and 5-fluorohexane in the ratio of 1.0 : 1.9 : 3.7 respectively, a small amount of 1-chloro-6-fluorohexane, and products (>5) which could not be identified. (Scheme 4.10)



(83) **(84C)** **F (84B)** **(84A)**

product ratio = 3.7 : 1.9 : 1.0 respectively

56%, 53% conv.

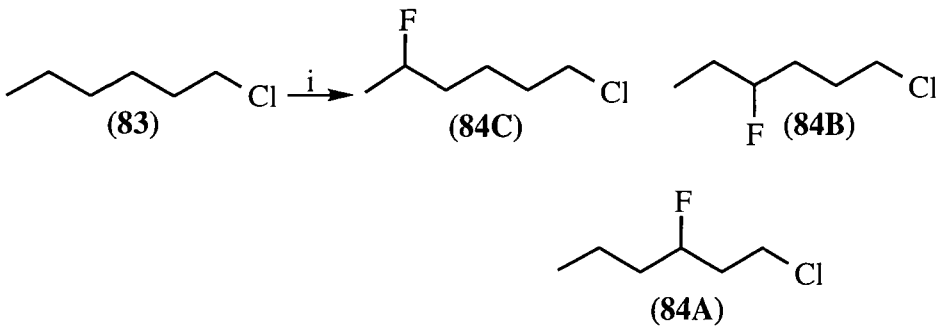
i = 1.1 Selectfluor^{TM}, CH_3CN, 82°C, 19.5 h.

Scheme 4.10

Preparative scale GC was used to isolate a sample of 1-chloro-4-fluorohexane (**84B**) and 1-chloro-5-fluorohexane (**84C**) as an isomeric mixture and the NMR spectra of this mixture were used (exactly as described for bromofluorohexane) to determine the identity of the products. The result was then extrapolated to predict that the other chlorofluorohexane in the crude product was 1-chloro-3-fluorohexane (**84A**).

4.4.4 Fluorination of 1-chlorohexane (83) using elemental fluorine

The direct fluorination of 1-chlorohexane (**83**) was carried out as usual and gave a crude product mixture which contained 1-chloro-3-, 4-, and 5-fluorohexane (**84A-C**) (22%, 72% conv.) in the ratio of 1.0 : 1.8 : 1.9 respectively, a small amount of 1-chloro-6-fluorohexane, products (>20) which could not be identified and tar (10%). (Scheme 4.11)



(83) **(84C)** **(84B)**

(84A)

product ratio = 1.9 : 1.8 : 1.0 respectively

22%, 72% conv.

i = 3 equiv. 10% F_2/N_2, CH_3CN, 0°C.

Scheme 4.11

The three major products from this reaction have the same ^{19}F NMR chemical shift values, mass spectra and retention times as the three major products from the Selectfluor™ reaction which is described above and, therefore, the products from this reaction were not isolated.

The low yield of products and the relatively large amount of tar which was obtained suggests that fluorination of 1-chlorohexane is a relatively unselective process. Most likely, this results because the secondary C-H bonds of the substrate are highly electron depleted by the chlorine atom which is a powerful electron withdrawing substituent (*cf.* direct fluorination of methyl valerate).

4.4.5 Summary of results

A summary of the results which are described in Section 4.4 is shown (Table 4.2).

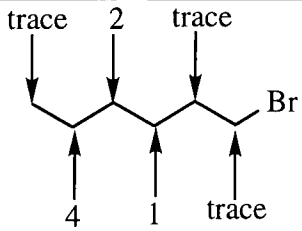
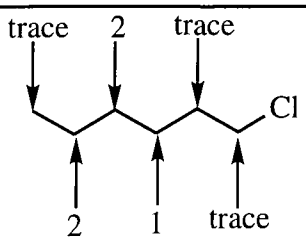
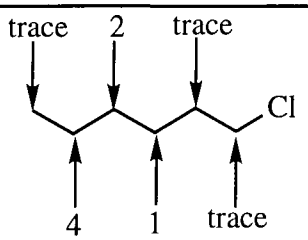
Substrate	Relative Selectivities at each Position using Elemental Fluorine	Relative Selectivities at each Position using Selectfluor™
1-Iodohexane **(80)**	no selective fluorination observed	no selective fluorination observed
1-Bromohexane **(81)**	no selective fluorination observed	
1-Chlorohexane **(83)**		

Table 4.2

Fluorination of 1-iodohexane **(80)** using both elemental fluorine and Selectfluor™ and fluorination of bromohexane **(81)** using elemental fluorine was not possible and, therefore, these results will not be discussed further.

Reaction of bromohexane **(81)** with Selectfluor™ results in fluorination of all secondary C-H bonds except those which are attached to C-1 and C-2. The same is also true for the fluorination of 1-chlorohexane **(83)** using both elemental fluorine and Selectfluor™.

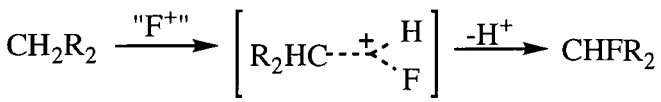
In general, fluorination of an alkyl chain which is attached to a halide atom gives a product distribution which is analogous to the product distribution that is obtained upon fluorination of an alkyl chain which is attached to a methyl ester.

4.6 Fluorination of both alkyl halide and methyl ester substrates : A summary

In summary, fluorination (using both elemental fluorine and Selectfluor^{TM}) of the alkyl chain which is attached to either a halide atom or a methyl ester is not affected significantly by the electron withdrawing group with the exceptions that:

- Fluorination of C-2 of a methyl ester does not occur.
- Fluorination of both C-1 and C-2 of an alkyl halide does not occur.
- Fluorination occurs preferentially at secondary sites that are furthest from the electron withdrawing group.

Reaction of a given substrate with both elemental fluorine and Selectfluor^{TM} gave product distributions which are very similar. In chapter 2 it was argued that if both fluorinating agents react with a given substrate to give the same product distribution it is likely that both reagents promote fluorination via the same mechanism. Therefore, the results which are outlined in this Chapter suggest that both elemental fluorine and Selectfluor^{TM} promote the fluorination of saturated C-H bonds via the same mechanism. An aliphatic electrophilic substitution mechanism (Scheme 4.12) was proposed in Chapter 2 and it is likely that the reactions which are outlined in this Chapter also proceed via this type of mechanism.



Scheme 4.12

4.7 Reaction of decyltrimethylsilane (85) with elemental fluorine

Having investigated the fluorination of various compounds which contain an electron withdrawing group attached to an alkyl chain, we then turned our attention to compounds which contain an electron releasing group attached to an alkyl chain.

We reasoned that direct fluorination of an alkylsilane should proceed in an analogous manner to the fluorination of an alkane compound but because the C-Si bond is both weaker and more polar than the C-H bonds (Table 4.3[2] and 4.4[131]), substitution of the trimethylsilane (TMS) group could, in principle, occur as shown (Scheme 4.13).

Atom	Electronegativity (Pauling Scale)
Carbon	2.5
Hydrogen	2.1
Silicon	1.8

Table 4.3

Bond type	Bond strength ($KJ\ mol^{-1}$)
C-H	413
C-Si	285

Table 4.4

$$R\text{-}SiMe_3 \xrightarrow[(F_2)]{'F^+'} R\text{-}F + F\text{-}SiMe_3$$

Scheme 4.13

Other workers have employed these principles for the preparation of selectively fluorinated aromatic compounds (Section 1.5.7.5; page 26).

We required an alkylTMS compound which would give, upon fluorination, a fluoroalkane which is relatively non-volatile but contains as few carbon atoms as possible (this minimises the possibility of C-H bond fluorination).

DecylTMS (**85**) was selected as the model substrate and was prepared as shown in Scheme 4.14.

$$RMgBr \xrightarrow{i} \underset{\textbf{(85)}}{RSiMe_3}$$

72%, 100% conv.

$R = C_{10}H_{21}$

i = $ClSiMe_3$,THF, 70°C, 30 min., N_2 atmosphere.

Scheme 4.14

The crude product was purified by distillation to give decylTMS in good yield and the pure product was characterised using standard techniques. This preparation was not optimised and it is likely that a higher yield could be obtained by moderating the reaction conditions.

Fluorination of decylTMS (**85**) was performed by passing elemental fluorine, as a 10% mixture with nitrogen, through a cooled, stirred mixture of the substrate and acetonitrile. After addition of all the fluorine, the reaction mixture was subject to a standard aqueous work-up and gave a crude product mixture which contained starting material (41 area %) and greater than 15 products which could not be identified. The ^{19}F NMR spectrum of the crude product contains a large number of signals. Particular attention was given to ascertaining (by reference to authentic samples) that neither decane nor 1-fluorodecane were present in the crude mixture.

Most of the products have a GC retention time which is slightly larger than the retention time of decylTMS (**85**). Invariably, fluoroalkanes have a retention time which is slightly greater than the corresponding alkane and, based on this fact, it is suspected that most of the products from this reaction are monofluorinated decylTMS derivatives.

It is probable that replacement of the TMS group by fluorine did not occur because the C-Si and C-H bonds have similar properties (i.e. bond strength and polarity). It is likely that reaction of elemental fluorine with compounds which contain a C-M bond that is more polar and/or weaker than the C-Si bond will result in selective fluorodemetallisation but, unfortunately, time did not permit further investigation of this area.

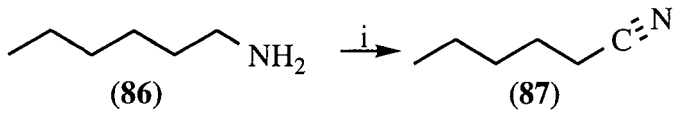
In conclusion, reaction of elemental fluorine with decylTMS results in unselective fluorination of the alkyl chain and, consequently, does not provide a route to selectively fluorinated alkane compounds.

4.8 Reaction of 1-aminohexane (86) with both elemental fluorine and Selectfluor^{TM}

Previous members of the Chambers group have investigated the reaction of elemental fluorine with various alkyl amines, which are an example of an alkyl chain with an electron releasing group attached. It was found that the amine group is oxidised to give the corresponding nitrile and we decided to expand the previous study by attempting the oxidation of 1-aminohexane (**86**) using both elemental fluorine and Selectfluor^{TM}.

Using elemental fluorine - passing 10% elemental fluorine through a solution containing 1-aminohexane (**86**) and acetonitrile gave, after a standard aqueous work-up, a crude product mixture which did not contain any fluorinated products (by ^{19}F NMR). Purification of the crude product by column chromatography on silica gel using dichloromethane as the eluent gave hexanenitrile (**87**) (44%, 100% conv.) (Scheme 4.15). However, it was noted that the crude product mixture also contained at least four other products (by GC-MS) which could be used to account for

approximately 50% of the starting material but, unfortunately, none of these products could be identified.



(86) (87)

i = 0.6 equiv. 10% F_2/N_2, CH_3CN, 0°C.

Scheme 4.15

Pure hexanenitrile (**87**) was characterised using NMR and IR spectroscopies, mass spectrometry, elemental analysis and boiling point determination. The product was easily identified as a nitrile because its IR spectrum contained a peak at 2245 cm^{-1} and its ^{13}C NMR spectrum contained a peak at δ_C = *ca.* 120 ppm, both are highly characteristic of nitrile functionality.

The mechanism of nitrile formation is not understood. If it is assumed that elemental fluorine is encouraged to act as an electrophile by the reaction medium then reaction may proceed via one of the following pathways, which are:

A) The amino-group activates the adjacent C-H bonds to electrophilic attack and fluorination of the alkyl chain results. In general, α-fluoroamine compounds are not stable and, therefore, the fluorinated product will eliminate hydrogen fluoride to give an imine. The whole sequence is then repeated to give nitrile. (Scheme 4.16)

$$RCH_2NH_2 \xrightarrow{"F^+"} RCHFNH_2 \xrightarrow{-HF} RHC{=}NH \xrightarrow[2.\ -HF]{1.\ +"F^+"} R{-}C{\equiv}N$$

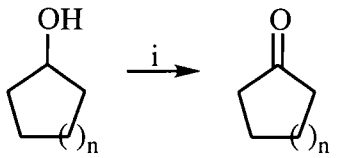
Scheme 4.16

B) Fluorination of the amino-group occurs to give an N-F type species which eliminates HF to give the corresponding imine. Further N-fluorination and elimination of hydrogen fluoride gives nitrile. (Scheme 4.17)

$$RCH_2NH_2 \xrightarrow{"F^+"} RCH_2NHF \xrightarrow{-HF} RHC{=}NH \xrightarrow[2.\ -HF]{1.\ +"F^+"} R{-}C{\equiv}N$$

Scheme 4.17

Previous work carried out by members of the Durham group has highlighted that reaction of elemental fluorine with secondary alcohols in acetonitrile results in preparation of the corresponding ketone (Scheme 4.18 shows some examples).[132]



n = 1; 76% (81% conv.)
n = 2; 76% (54% conv.)

i = 10% F_2/N_2, CH_3CN, 3°C.

Scheme 4.18

It was proposed that reaction proceeds through a hypofluorite-type species as shown (Scheme 4.19) and this reaction mechanism is exactly analogous to the pathway shown in Scheme 4.17.

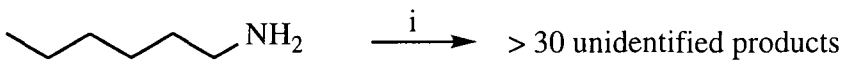
$$RCH_2OH \xrightarrow{"F^+"} RCH_2OF \xrightarrow{-HF} RHC{=}O$$

Scheme 4.19

Therefore, it is likely that oxidation of aminohexane (**86**) using elemental fluorine proceeds via formation of an N-F type complex.

In conclusion, the amine functionality of 1-aminohexane does not direct fluorination to the alkyl chain of the substrate but, instead, oxidation of the functional group occurs. In the context of the present study, it has been shown that the amine group is not compatible with elemental fluorine but, in a different context, the selective oxidation of amine to nitrile could be highly advantageous.

Using Selectfluor^{TM} - stirring a mixture which contained a small excess of Selectfluor^{TM}, 1-aminohexane (**86**) and anhydrous acetonitrile gave, after 5 minutes and a standard aqueous work-up, a crude product mixture which contained more than thirty unidentified products. (Scheme 4.20)



(86)

i = 1.1 Selectfluor^{TM}, CH_3CN, 5 min., -10°C.

Scheme 4.20

This reaction was repeated at 0, 20 and -40°C and in each case gave a very similar result to the reaction which was carried out at room temperature. Consequently, reaction of Selectfluor^{TM} with aminohexane (**86**) was not pursued further.

4.9 Conclusions

In summary, both elemental fluorine and Selectfluor^{TM} can be used to selectively fluorinate hydrocarbon derivatives that contain an electron withdrawing group. In general, fluorination of the hydrocarbon derivative is not affected significantly by the EWG.

For a given substrate, reaction with both elemental fluorine and Selectfluor^{TM} gives a very similar product distribution and this indicates that both reagents promote fluorination via the same mechanism.

An alkylTMS (**85**) derivative was prepared and reacted with elemental fluorine in the hope that fluordesilylation would result. Unfortunately, a large number of fluorinated products were obtained and this demonstrates that selectively fluorinated alkane compounds can not be prepared via this route.

1-Aminohexane (**86**) can be oxidised to the corresponding nitrile using elemental fluorine and this reaction illustrates the use of elemental fluorine for the preparation of compounds which do not contain fluorine. In contrast, reaction of Selectfluor^{TM} with aminohexane (**86**) results in a highly unselective reaction.

Chapter 5: Fluorination of Heteroaromatic Compounds

5.1 Introduction

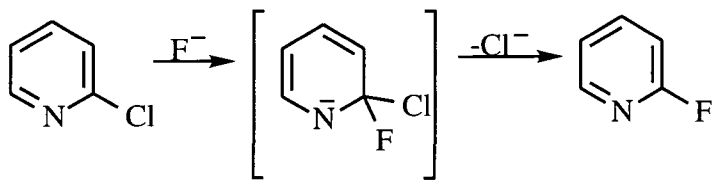
This Chapter is concerned with the preparation of selectively fluorinated N-containing heteroaromatic compounds using fluorine-iodine mixtures. Previous work carried out by members of the Chambers group in Durham has established that fluorine-iodine mixtures can be used to fluorinate heteroaromatic compounds, such as pyridine, quinoline and phenanthridine derivatives. Following this work we aimed to demonstrate that the methodology could also be used to fluorinate quinoxaline and diazine derivatives.

5.2 Preparation of selectively fluorinated heteroaromatic compounds

There are relatively few methods which can be used to prepare selectively fluorinated heteroaromatic compounds and the most important procedures are outlined briefly below.

5.2.1 Halex Reactions[133]

Halex reactions involve replacement of a chlorine substituent by fluorine and are usually carried out using an alkali metal fluoride as the source of fluoride ion. Reaction proceeds via a nucleophilic aromatic substitution mechanism (Scheme 5.1). Consequently, fluorination of many heteroaromatic compounds proceeds more readily than the corresponding carbocyclic derivative because the heteroaromatic ring is both less electron rich (and therefore more susceptible to nucleophilic attack) and more efficient at stabilising the anionic intermediate.



Scheme 5.1

The lattice energy of the alkali metal fluorides increases according to the series:

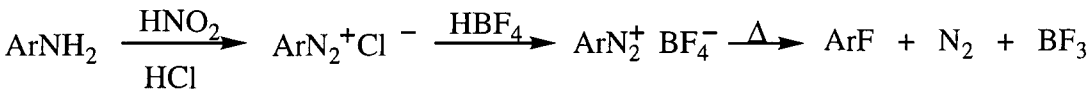
CsF<RbF<KF<NaF<LiF

Therefore, caesium fluoride is the most efficient source of fluoride ion of the series but both caesium and rubidium fluoride are expensive and this means that potassium fluoride is often the reagent of choice for Halex reactions.

Other sources of fluoride ion, such as hydrogen fluoride[134], tetraalkylphosphonium hydrogen difluoride[135] and caesium fluoride/18-crown-6[136] have also be employed to prepare selectively fluorinated heteroaromatic compounds.

5.2.2 Fluorodediazonisation[133]

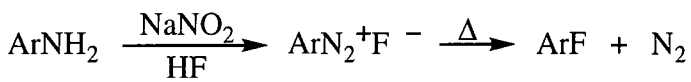
The Balz-Schiemann reaction involves diazotization of an aromatic amine to give the corresponding diazonium tetrafluoroborate which is then decomposed thermally to give fluoroaromatic, nitrogen, and boron trifluoride (Scheme 5.2).



Scheme 5.2

The intermediate diazonium tetrafluoroborate must be isolated, washed and then dried before it is decomposed and care must be taken during the decomposition step because the reaction is exothermic.

Alternatively, fluoroheteroaromatic compounds can be prepared via the diazonium fluoride (Scheme 5.3) and this process has the advantage that the intermediate salt need not be isolated prior to decomposition.



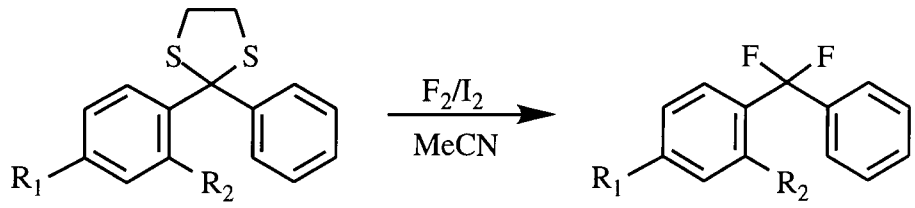
Scheme 5.3

5.2.3 Direct fluorination

Both the Halex and the fluorodediazonisation routes to fluoroheteroaromatic compounds depend on the availability of the appropriate derivatised heteroaromatic but, in contrast, elemental fluorine can be used to convert various parent heteroaromatic compounds directly to the selectively fluorinated products and Chapter 1 (Section 1.5.7.6; page 30) contains a review of this area.

5.3 Reaction of fluorine-iodine mixtures with organic compounds

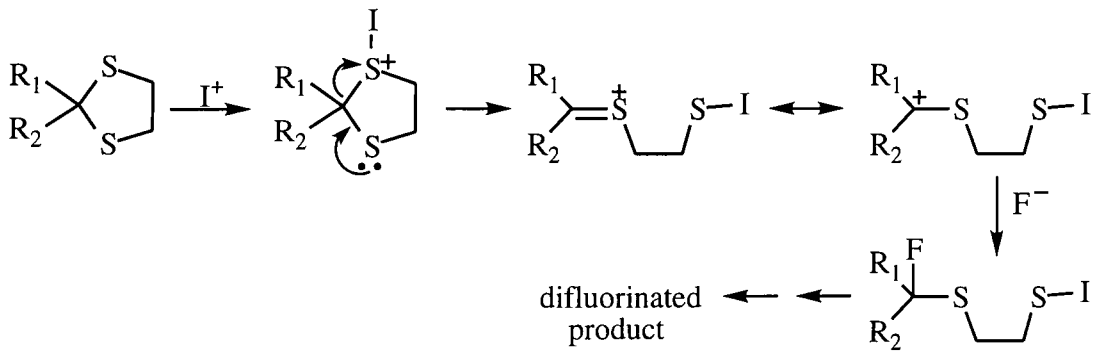
Previous work[137] by members of the Durham group has shown that diaryl 1,3-dithiolanes can be converted to the corresponding *gem*-difluoride by passing elemental fluorine through a solution containing thiolane substrate and iodine in acetonitrile. (Scheme 5.4)



when R_1,R_2= Me; yield=81%
when R_1=NO_2, R_2=H; no reaction

Scheme 5.4

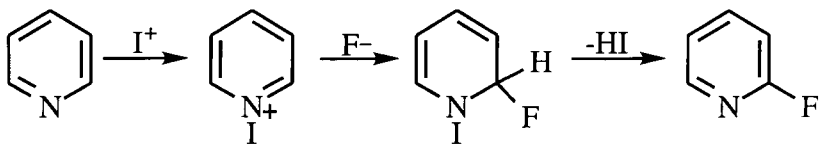
It was noted that the presence of electron donating substituents on the aromatic ring promotes fluorodesulfurisation, whereas, the presence of electron withdrawing substituents inhibits the fluorination reaction. It was proposed that the fluorine iodine-mixture provides a source of both iodonium and fluoride ions and iodination of sulfur by iodonium ion activates the substrate towards attack by fluoride ion (Scheme 5.5).



Scheme 5.5

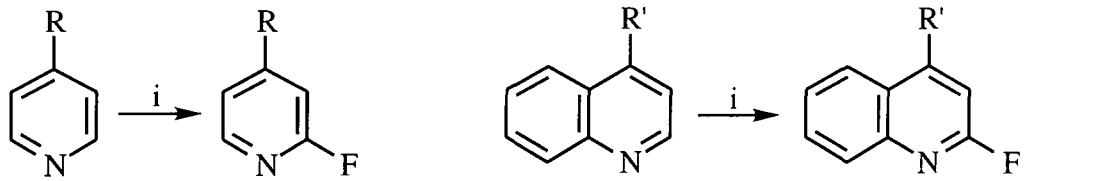
From the above fluorodesulfurisation results it was reasoned that if an N-containing heteroaromatic compound was employed in place of the S-containing substrate, it is likely that iodonium ion would complex with the nitrogen. Such complexation would activate the adjacent carbon atom to fluoride ion attack and the resulting intermediate should eliminate hydrogen iodide to effect re-aromatisation

(Scheme 5.6). The net result of this reaction is, of course, replacement of hydrogen by fluorine.



Scheme 5.6

This reasoning was extrapolated and previous work by members of our group has shown that a range of pyridine and quinoline derivatives can be selectively fluorinated using fluorine-iodine mixtures. (Scheme 5.7 shows some examples)



R=H; 56% (59% conv.)
R=Et; 54% (78% conv.)

R'=H; 54% (77% conv.)
R'=Me; 49% (58% conv.)

i = 10% F_2/N_2, I_2, NEt_3, $CF_2ClCFCl_2$, 0°C.

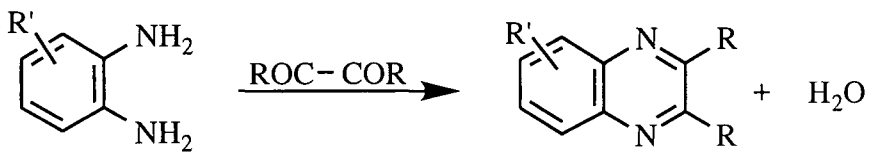
Scheme 5.7

We then decided to further investigate the scope of this reaction and have attempted the selective fluorination of both quinoxaline and diazine systems using fluorine-iodine mixtures. The results of this investigation will now be outlined.

5.4 Preparation and fluorination of quinoxaline derivatives

5.4.1 Preparation of quinoxaline derivatives

Quinoxaline derivatives which have a substituent on the benzo-fused ring are not available commercially but can be prepared by condensation of an aromatic *o*-diamine with a 1,2-dicarbonyl compound (Scheme 5.8).



Scheme 5.8

This procedure can be applied to a wide range of substituted *o*-diamine derivatives[138] and, consequently, it was used to prepare a range of substituted quinoxalines (Table 5.1). All quinoxaline compounds were purified using distillation, recrystallisation or sublimation and characterised using standard techniques.

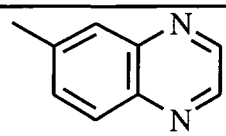
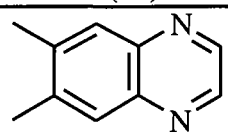
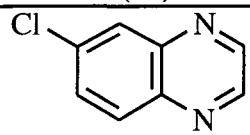
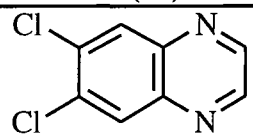
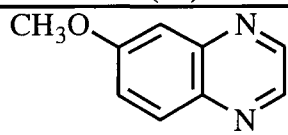
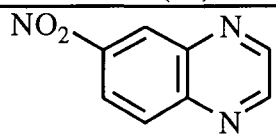
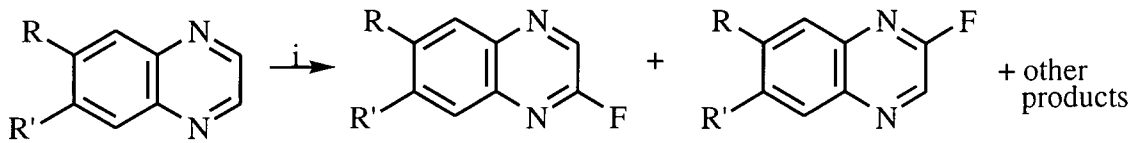
Quinoxaline Derivative	Yield[a] %
 **(88)**	73
 **(89)**	78
 **(90)**	79
 **(91)**	78
 **(92)**	82
 **(93)**	89

Table 5.1

[a]Yield corresponds to pure, isolated product.

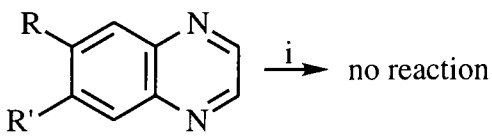
5.4.2 Preparation of fluoroquinoxaline derivatives

Passing a small excess of elemental fluorine, as a 10% mixture with nitrogen, through a stirred, cooled (0°C) solution of quinoxaline, iodine and triethylamine* in 1,1,2-trichlorotrifluoroethane (Scheme 5.9) gave, after a standard aqueous work-up, a crude product. The amount of fluoroquinoxaline and the amount of starting material in the crude product was determined using ^{19}F NMR spectroscopy and GC-MS and the procedure which is detailed in Section 2.3.1 (page 44). (Table 5.2)



(88-90, 92, 94) **(95-99)**

R=R'=H; R=Me, R'=H
R=R'=Me; R=Cl, R'=H
R=MeO, R'=H



(91, 93)

R=R'=Cl; R=NO_2, R'=H

i = 1.5 equiv. 10% F_2/N_2, I_2, NEt_3, $CF_2Cl\text{-}CFCl_2$, 0°C.

Scheme 5.9

* Triethylamine was added to complex with hydrogen iodide.

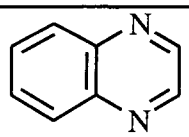
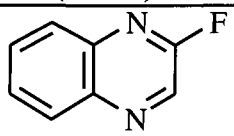
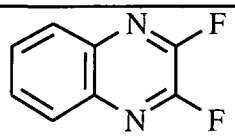
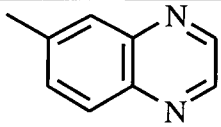
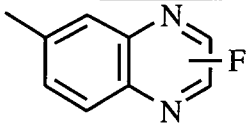
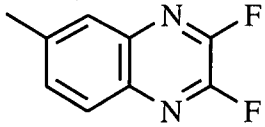
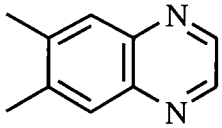
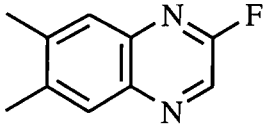
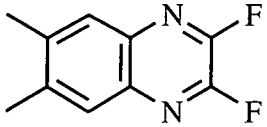
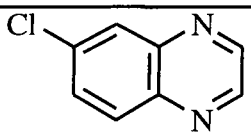
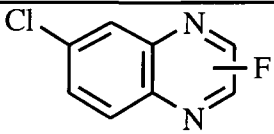
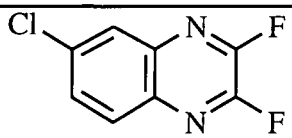
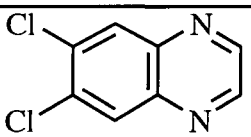
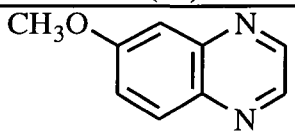
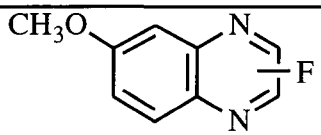
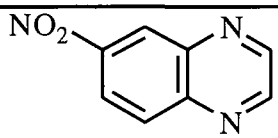
Starting Material	Fluoroquinoxaline Yield (Conv.) /%	Difluoroquinoxaline Yield /%
 **(94)**	 **(95)** 48 (91)	 **(100)** 11
 **(88)**	 **(96A, B)** 45 (43)	 **(101)** 7
 **(89)**	 **(97)** 40 (75)	 **(102)** 5
 **(90)**	 **(98A, B)** 44 (64)	 **(103)** 3
 **(91)**	0 (0)	-
 **(92)**	 **(99A, B)** 43 (55)[a]	-
 **(93)**	0 (0)	-

Table 5.2

[a] Not isolated.

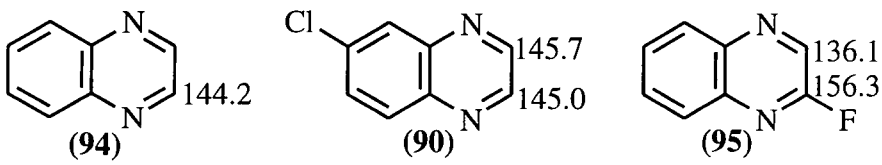
Pure fluoroquinoxaline derivatives were isolated by column chromatography on silica gel using dichloromethane as the eluent and were characterised using standard techniques.

It is interesting to note that both 6-nitroquinoxaline (**93**) and 6,7-dichloroquinoxaline (**91**), which both contain strong electron withdrawing groups, could not be fluorinated using this methodology. However, fluorination of all other quinoxaline derivatives which were investigated proceeds smoothly and gave fluorinated quinoxaline in reasonable yield.

In most cases, a small amount of the corresponding 2,3-difluorinated quinoxaline was also obtained and these products will be discussed in more detail in the next section.

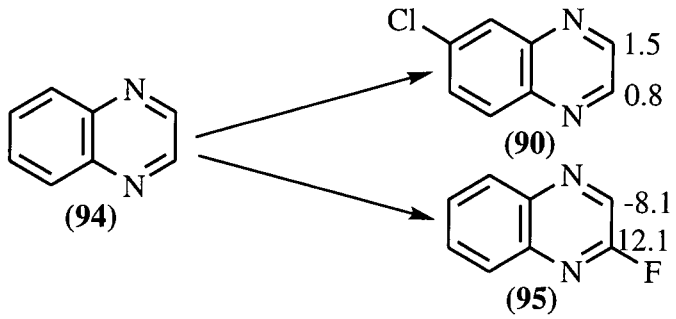
Chlorofluoroquinoxaline (98A, B) - Fluorination of 6-chloroquinoxaline (**90**) gave an isomeric mixture of 6-chloro-2-fluoroquinoxaline (**98A**) and 7-chloro-2-fluoroquinoxaline (**98B**) (in the ratio of *ca.* 1.8 : 1.0) and it was not possible to separate these isomers using standard separation methods. However, the ^{13}C (and therefore the ^{19}F and ^{1}H) NMR spectra of the isomeric mixture was fully assigned and it was possible to determine which of the two isomers was the major. What follows is a description of the procedure which was used to assign the ^{13}C NMR spectrum of the pure isomeric mixture.

The assignment of C-2 and C-3 was carried out initially for two reasons. Firstly, the chemical shifts values of these two positions can be predicted using substituent effects and the ^{13}C chemical shift values of quinoxaline (**94**)[139], 6-chloroquinoxaline (**90**)[140] and 2-fluoroquinoxaline (**95**) (Scheme 5.10) were considered to achieve this.



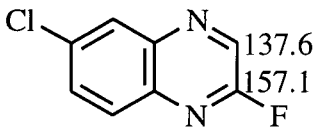
Scheme 5.10

The difference in chemical shift values between quinoxaline and the quinoxaline derivatives is shown (Scheme 5.11).

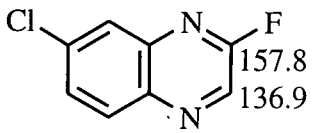


Scheme 5.11

Predicted ^{13}C chemical shift values (Scheme 5.12) for the two chlorofluoroquinoxaline compounds were calculated using the values which are shown in Scheme 5.11.



6-Chloro-2-fluoroquinoxaline
(98A)



7-Chloro-2-fluoroquinoxaline
(98B)

Scheme 5.12

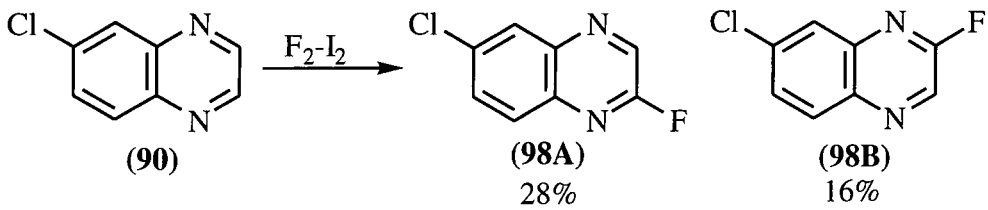
The second reason for the initial assignment of C-2 and C-3 is that both carbon atoms show a distinct C-F coupling pattern. Carbon atoms which are bonded to a fluorine atom display a very large coupling constant (*ca.* 250 Hz), whereas, two bond C-F coupling constants are much smaller (*ca.* 40Hz). Therefore, it is very easy to identify C-2 and C-3 of both isomers in the ^{13}C NMR spectrum.

Predicted and observed chemical shift values for both isomers are shown (Table 5.3) and from this information it is clear that the major isomer is 6-chloro-2-fluoroquinoxaline **(98A)**.

Isomer	Carbon	Observed chemical Shift (ppm)	Predicted Chemical Shift (ppm)
Major	2	156.7	157.1
	3	137.4	137.6
Minor	2	157.2	157.8
	3	136.5	136.9

Table 5.3

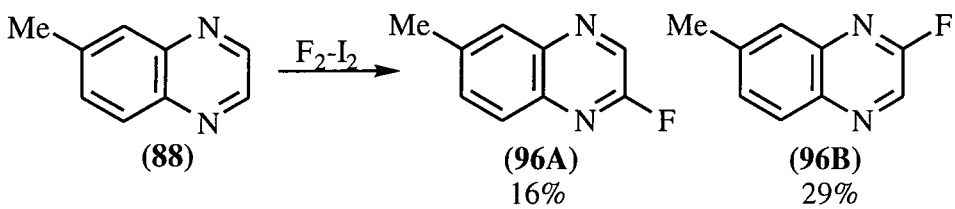
In conclusion, fluorination of 6-chloroquinoxaline (**90**) using a mixture of fluorine and iodine gave 6-chloro-2-fluoro- (**98A**) and 7-chloro-2-fluoroquinoxaline (**98B**) in the ratio of 1.8 : 1.0 respectively (Scheme 5.13).



(**90**) (**98A**) 28% (**98B**) 16%

Scheme 5.13

Fluoromethylquinoxaline (96A, B) - The above procedure was also applied to the isomeric product mixture which was obtained from the 6-methylquinoxaline (**88**) reaction. It was found that the mixture contained 2-fluoro-6-methyl- (**96A**) and 2-fluoro-7-methylquinoxaline (**96B**) in the ratio of 1.0 : 1.8 respectively (Scheme 5.14).



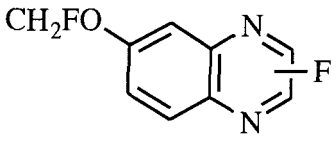
(**88**) (**96A**) 16% (**96B**) 29%

Scheme 5.14

6-Methoxyquinoxaline (92) - Fluorination of 6-methoxyquinoxaline (**92**) gave a crude product mixture which contained (based on GC-MS and ^{19}F NMR analysis) 2-fluoro-6-methoxyquinoxaline (**99A**) and 2-fluoro-7-methoxyquinoxaline (**99B**) (43%, 55% conversion). Unfortunately, attempts to isolate the monofluorinated products proved unsuccessful and the final 'purified' product

contained 2-fluoro-6-methoxyquinoxaline (**99A**), 2-fluoro-7-methoxyquinoxaline (**99B**), and impurities (11% by GC).

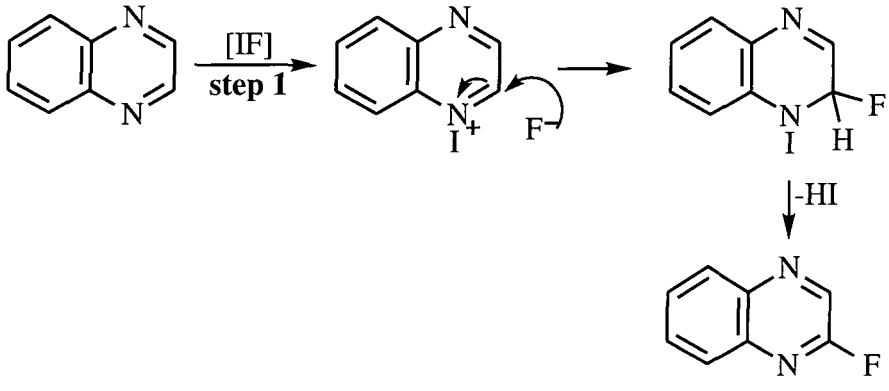
The ^{19}F NMR spectrum of the product contains two triplets at *ca.* δ_F=-151 ppm which both have a coupling constant of approximately 56Hz. Given that $-OCH_2F$ is observed in this region and as a triplet with a coupling constant of *ca.* 50Hz, it is highly likely that the identity of the impurity is as shown (**A**).



(A)

5.4.3 Mechanism of the fluorination reaction

The proposed mechanism for the fluorination reaction is shown (Scheme 5.15).



Scheme 5.15

It is probable that both nitro- (**93**) and dichloroquinoxaline (**91**) do not have sufficient base strength to facilitate step 1 of the proposed mechanism and, therefore, these substrates cannot be fluorinated using a mixture of fluorine and iodine.

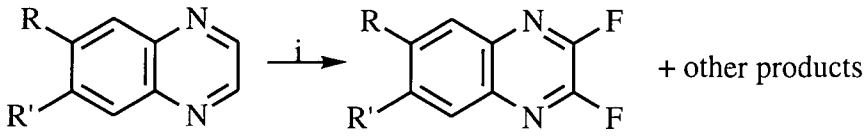
The product distribution obtained upon fluorination of both 6-methyl- (**88**) and 6-chloroquinoxaline (**90**) can also be explained using this mechanism.

In 6-chloroquinoxaline (**90**) N-1 is at a greater distance from the chlorine substituent than N-4 and, therefore, the negative inductive effect of chlorine is stronger at N-4. This means that iodination of N-1 is favoured over complexation of N-4 and, therefore, subsequent attack by fluoride ion occurs at C-2 predominantly.

In contrast, the positive inductive effect of the methyl substituent in 6-methylquinoxaline (**88**) leads to a larger amount of 2-fluoro-7-methylquinoxaline (**96B**) .

5.4.4 Preparation of difluoroquinoxaline derivatives

A series (Table 5.4) of 2,3-difluorinated quinoxaline derivatives was prepared using the fluorination procedure which is described above and a large excess of elemental fluorine (Scheme 5.16).



(94, 88-90) **(101-103)**

R=R'=H; R=Cl, R'=H
R=Me, R'=H; R=R'=Me

i = 3 equiv. 10% F_2/N_2, I_2, 2 NEt_3, $CF_2Cl\text{-}CFCl_2$, 0°C.

Scheme 5.16

Quinoxaline	Yield of monofluorinated product(s)[a] %	Yield of difluorinated product[a] %	Conversion %[a]
Quinoxaline (**94**)	8	33	100
6-Methyl (**88**)	16	23	71
6,7-Dimethyl (**89**)	14	12	90
6-Chloro (**90**)	25	19	94

Table 5.4

[a] After work-up. Values were determined as described in Section 5.4.2.

Pure difluoroquinoxaline derivatives were isolated by column chromatography on silica gel using 1:1 dichloromethane-hexane as the eluent and were characterised using standard techniques.

It is interesting to note that the total yield of fluorinated products decreased as the relative amount of fluorine which was passed through the reaction mixture was increased (*cf.* yields shown in Table 5.2 and Table 5.4).

5.5 Attempted fluorination of diazine compounds

The selective fluorination of the diazine compounds pyridazine (**104**), pyrimidine (**105**) and pyrazine (**106**) was also attempted using a mixture of fluorine and iodine. However, only a trace amount of the corresponding fluoroheteroaromatic compound was obtained in each crude product mixture (by GC-MS) and this result is very surprising.

The pK_a values of pyridazine (**104**), pyrimidine (**105**), pyrazine (**106**), and quinoxaline (**94**) are 2.33, 1.31, 0.65 and 0.56 respectively (all determined in water between 20 and 30°C)[141]. If the pK_a values for the diazine compounds are compared with the corresponding value for quinoxaline it is apparent that iodination of a diazine nitrogen atom should occur more readily than iodination of a quinoxaline and, at present, it is not clear why these fluorination reactions were unsuccessful.

5.6 Alternative solvents

5.6.1 Introduction

The 1990 Montreal Protocol bans the production of trichlorotrifluoroethane (Freon 113)[107] and Freon 113 was employed as the reaction solvent in all of the experiments which are outlined in this Chapter. Therefore, the fluorination methodology cannot be implemented further unless an alternative reaction solvent can be identified.

Consequently, the objective of the work outlined in the next section was to identify a reaction solvent which will facilitate the fluorination of heteroaromatic compounds using fluorine-iodine mixtures.

5.6.2 Results of solvent survey

A number of reaction solvents were identified as possible alternatives to Freon 113 and the direct fluorination of quinoxaline (**94**) (or 4-ethylpyridine (**107**)) was attempted in each one.

Fluorination reactions were attempted exactly as for the fluorination of quinoxaline (**94**) in Freon 113 and the results obtained are summarised (Table 5.5).

Solvent	Conversion %	Yield of mono- (di-) fluorinated products %
α,α,α-Trifluoromethylbenzene	76	6 (<1)
Dichloromethane	0	0
Dimethylformamide	0	0
Hexafluorobenzene	49	26 (6)
Nitromethane	0	0
Tetrahydrofuran	0	0
Freon 113	91	48 (11)

Table 5.5

Table 5.5 shows that all product mixtures contained a smaller amount of fluoroquinoxaline (**95, 100**) than the corresponding reaction which was performed using Freon 113 as the solvent. However, the reaction which was performed in hexafluorobenzene resulted in a significant quantity of fluoroquinoxaline (**95, 100**) and, after full optimisation of the reaction conditions, it may be feasible to perform the fluorination of heteroaromatic compounds in this solvent.

5.7 Conclusions

The selective fluorination of quinoxaline derivatives can be accomplished using fluorine-iodine mixtures. However, quinoxaline compounds which are relatively electron deficient and the diazine compounds pyridazine (**104**), pyrimidine (**105**) and pyrazine (**106**) can not be fluorinated using this methodology.

Freon 113 was employed as the reaction solvent but this solvent is now banned and, therefore, an alternative is required.

A solvent survey highlighted that hexafluorobenzene may be a possible alternative to Freon 113 but reactions which were carried out in the former solvent are largely inferior to those carried out in the latter.

In contrast to the main methods that are used to prepare selectively fluorinated heteroaromatic compounds, the interhalogen methodology described in this Chapter provides a direct route from various parent heteroaromatic compounds to the corresponding fluorinated products.

The Use of Elemental Fluorine in the Laboratory

Elemental fluorine is extremely reactive and very toxic and, consequently, it is necessary to use apparatus which has been designed specifically to carry out direct fluorination reactions. What follows below is a description of the procedures and equipment which are used by the Durham group to perform reactions using elemental fluorine.

Elemental fluorine is purchased as a 50% mixture with nitrogen in large cylinders (*ca.* 51 l) (referred to as **C1**) which contain *ca.* 1 kg of elemental fluorine.

C1 is housed in a vented gas cabinet and is connected to a manifold system (Figure 1) via a metal-metal connection. It is important that organic materials, such as PTFE, are not used in this connection as reaction of elemental fluorine with such materials is possible because of the relatively high pressure and high concentration of fluorine at this point.

The manifold system is equipped with a pneumatic shut-off valve that can be operated remotely if required and a bellows valve which is used to reduce the pressure of the fluorine-nitrogen mixture to *ca.* 4 atm (the pressure inside in **C1** when it is full is *ca.* 27 atm).

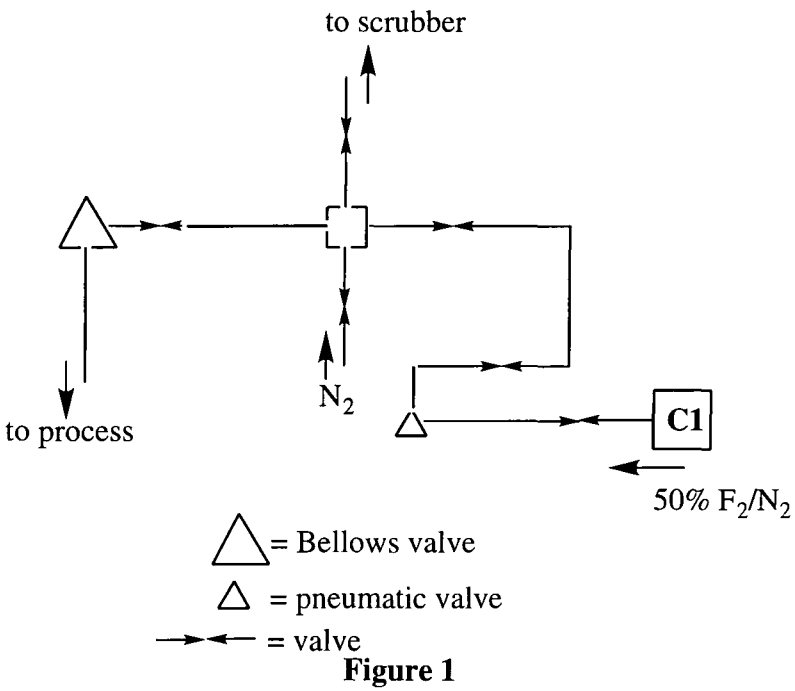


Figure 1

After the initial installation of the Bellows valve it is not adjusted and this minimises disruption of the surface passivation which helps to protect the valve from degradation by fluorine.

Fluorine is supplied from **C1** via 1/4" stainless steel tubing to a rig (Figure 2) which is constructed from 1/4" stainless tubing, Monel® or stainless steel Swagelok® valves* and stainless steel fittings and is housed in a stainless steel fumes cupboard.

This rig can be used to fill smaller cylinders (usually 3.7 l) which are then transferred to other fumes cupboards which house smaller fluorination rigs (Figure 3) (see later). Alternatively, the rig shown in Figure 2 can be used to perform fluorination reactions.

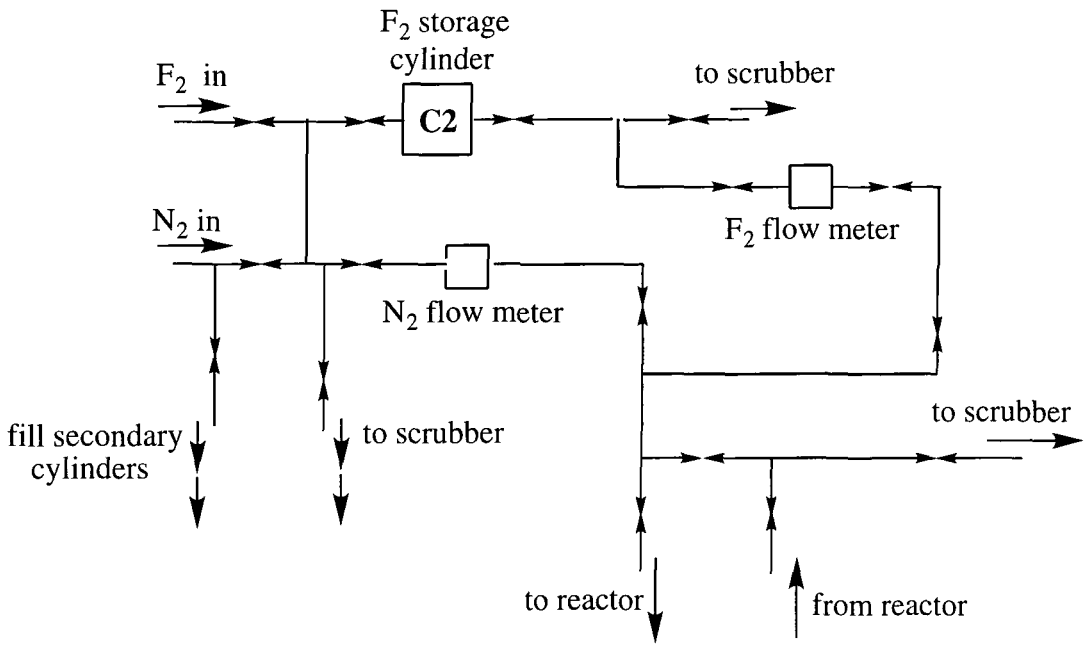


Figure 2

When filling smaller cylinders with fluorine from **C1** two members of the group must be present and each person must be equipped with a face-shield and nitrile or PVC gauntlets (in addition to the standard personal protective equipment which is worn in a laboratory).

To perform fluorination reactions using the rig shown in Figure 2, the fluorine storage cylinder (**C2**) is filled with fluorine (from **C1**) and then fluorine is run from **C2** into a reaction vessel. The flow of gaseous reagent into the reactor is monitored using a flow meter (which operates using the principle of thermal mass) and the flow rate is controlled using a metering valve.

* Typical valve types include Metering, Severe Service Union Bonnet, and Integral Bonnet Needle Valves.

Under no circumstances are reactions performed using fluorine directly from **C1**.

Small fluorination rigs (shown in Figure 3) are constructed from stainless tubing and fittings and stainless steel or Monel® valves and, again, a flow meter/metering valve is used to control the flow of gas from the rig.

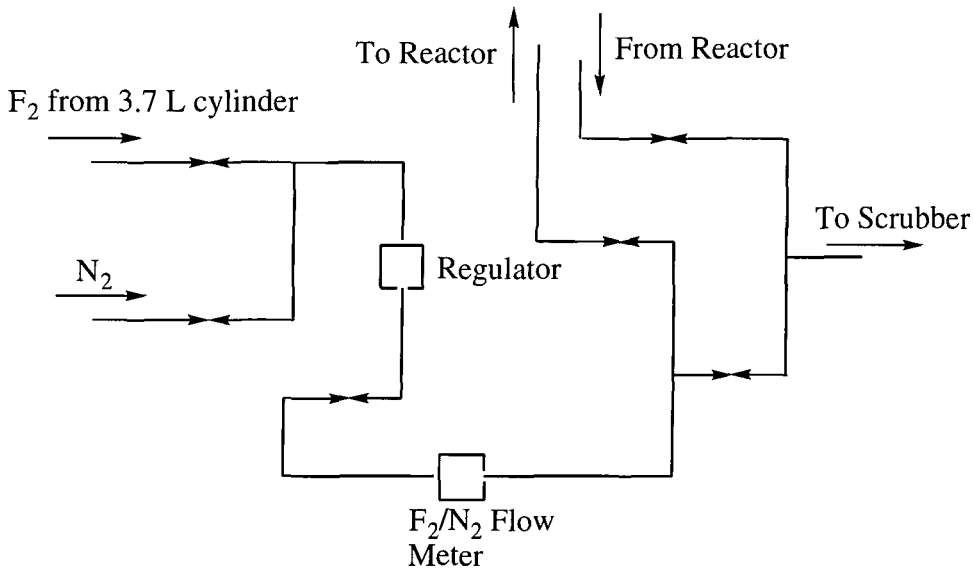


Figure 3

New valves contain a lubricant which is not compatible with elemental fluorine and, therefore, valves are degreased using dichloromethane and then re-greased with a perfluorocarbon-based lubricant.

All valves, tubing, fittings, and cylinders which are used to handle fluorine are passivated using fluorine before they are used to perform fluorination reactions.

All fluorination reactions which are described in this Thesis were carried out in a glass reactor (Figure 4) which was fitted with a stainless steel entrainment stirrer that allows the gas inside the reactor to re-circulate. The stirrer was fitted into a glass stirrer guide which is situated in the centre of the base of the reactor. The stirrer was powered by a IKAMAG motor which is capable of rotating the stirrer at 2000 rpm. The reaction mixture was cooled using a salt bath and the external coil of a HAAKE cryostat which contained synth 60 coolant.

Fluorine was supplied to the bottom of the reaction vessel using a PTFE dip-pipe and exit gases were piped from the reactor to a scrubbing tower which was filled with soda lime.

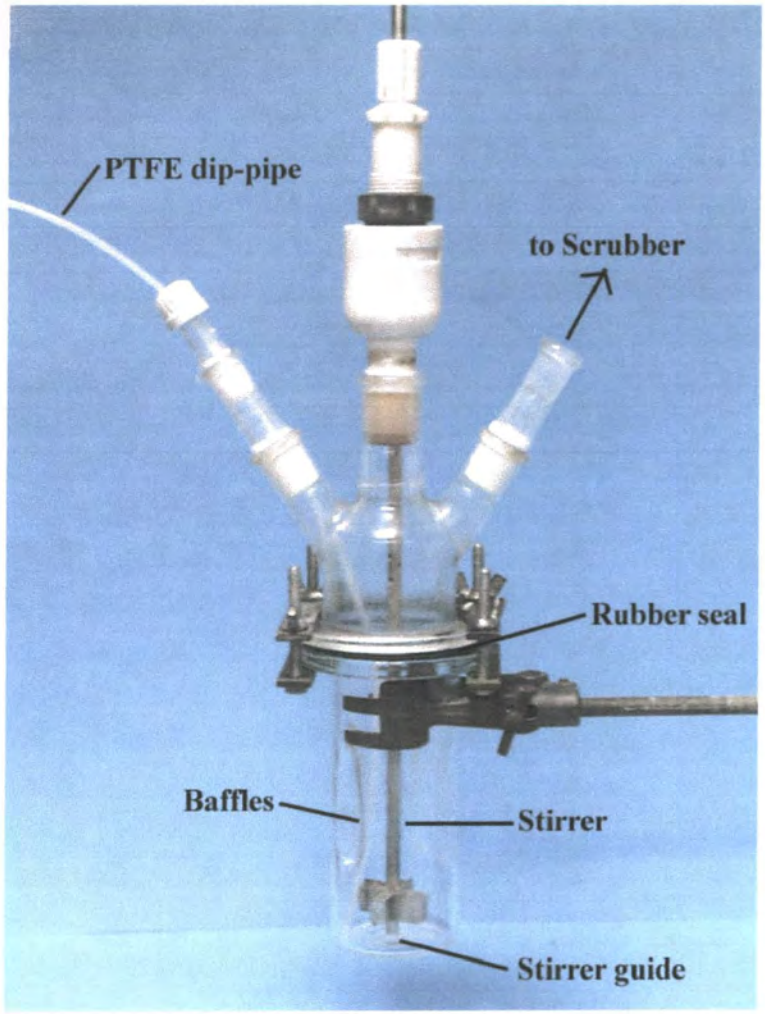

PTFE dip-pipe
to Scrubber
Rubber seal
Baffles
Stirrer
Stirrer guide

Figure 4

Reagents and Instrumentation

Reagents and solvents

All chemicals were used as received from the suppliers unless otherwise stated. Solvents were dried using standard methods and stored over molecular sieves where appropriate.

Melting points

Melting points were carried out at atmospheric pressure using a Gallenkamp apparatus and are uncorrected.

Boiling points

Boiling points were either recorded during distillation or determined at atmospheric pressure (Siwoloboff's method) using a Gallenkamp apparatus and are uncorrected.

Gas Liquid Chromatography

Chromatography was performed on a Hewlett Packard 5890 Series II gas liquid chromatograph equipped with a 25m cross-linked methyl silicone or 5% phenyl methyl silicone capillary column. Preparative scale GC was performed on a Shimadzu GC-8A gas chromatograph equipped with a thermal conductance detector and a 4m SE30 packed column.

Elemental Analyses

Elemental analyses were carried out on an Exeter Analytical CE-440 elemental analysis machine.

NMR Spectra

NMR spectra were recorded in deuteriochloroform on either a Bruker AC 250, a Varian Gemini 200, a Varian Mercury 200, a Varian VXR 400S or a Unity Inova 500 NMR spectrometer using trimethylsilane and trichlorofluoromethane as internal standard. Coupling constants are given in Hz and in ^{19}F NMR spectra, upfield shifts are quoted as negative.

Mass Spectra

Mass spectra were recorded on a Fisons VG Trio 1000 spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. Accurate mass measurements

were determined on a Micromass Autospec Mass Spectrometer or at the EPSRC Mass Spectrometry Service Centre, Swansea.

FT-IR Spectra

IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer using thin films between KBr or NaCl plates as either neat liquids or as Nujol mulls.

Chapter 6: Experimental to Chapter 2

6.1 Solvent survey using *cis*-decalin (46)

General procedure. A mixture containing *cis*-decalin (**46**) and the solvent was placed in the fluorination apparatus (as detailed above) and elemental fluorine, as a 10% (v/v) mixture with nitrogen, was passed through the stirred, cooled (0°C) mixture at *ca.* 50 cm^3min^{-1} using PTFE tubing. Preceding and following fluorination, the reaction mixture was purged with nitrogen. After the final nitrogen purge, the resulting mixture was poured into water, neutralised ($NaHCO_3$), and extracted using dichloromethane (3 x 40 cm^3). The combined, dried ($MgSO_4$) organic extracts were evaporated to give a crude product. Distillation of this mixture gave a colourless crude product mixture and, in some cases, a brown solid residue (tar) remained in the distillation vessel. The amount of *cis*-9-fluorodecalin (**47**) which was present in the crude product was determined by adding a known amount of fluorobenzene to a known amount of crude product and then analysing the resulting mixture using ^{19}F NMR spectroscopy. The amount of starting material which remained after the reaction was calculated by relating the amount of fluorodecalin to the amount of decalin using the gas chromatograph of the crude product. GC response factors were taken into consideration when performing the latter calculation. In some cases, '% area' values have been given in the following text. These values correspond to the relative peak area of a given product in the gas chromatograph of the crude product mixture. It should be noted that response factors were not calculated for products which were not isolated and, therefore, '% area' values quoted for such products should be taken as approximate.

Tar amounts are quoted as a weight percentage relative to the amount of *cis*-decalin used in the reaction.

Acetonitrile (substrate : fluorine = 1:1). *cis*-Decalin (**46**) (4.9 g, 36 mmol), elemental fluorine (38 mmol), and anhydrous acetonitrile (140 cm^3) gave a pale yellow crude product mixture (8.3 g) which contained *cis*-decalin (**46**) (87 area %), *cis*-9-fluorodecalin (**47**) (9 area %); data as above, unsaturated decalin derivatives (1 area %); data as above and unidentified products (3 area %).

Acetonitrile (substrate : fluorine = 1:5). *cis*-Decalin (**46**) (3.0 g, 22 mmol), elemental fluorine (110 mmol), and anhydrous acetonitrile (140 cm^3) gave a yellow crude product (7.4 g) which contained *cis*-9-fluorodecalin (**47**) (1.3 g, 57%, 64% conv.), difluorodecalin (5 area %); *m/z* (EI^+) 174 (M^+, 66%), 154 (44, M^+-HF), unsaturated decalin derivatives (2 area %); *m/z* (EI^+) 136 (M^+, 100%) and unidentified products. Purification of the crude product by preparative scale GC gave an analytically pure sample of *cis*-9-fluorodecalin (**47**) as a colourless liquid; bp 202-

203°C (Found: C, 76.7; H, 11.1. $C_{10}H_{17}F$ requires: C, 76.9; H, 11.0%); NMR spectrum no. 2[108] ; Mass spectrum no. 2; IR spectrum no. 2.

Acetonitrile (substrate : fluorine = 1:16). *cis*-Decalin (**46**) (2.6 g, 19 mmol), elemental fluorine (299 mmol), and anhydrous acetonitrile (140 cm^3) gave a dark brown crude product mixture (5.5 g) which contained *cis*-decalin (**46**) (1 area %), *cis*-9-fluorodecalin (**47**) (10 area %); data as above, difluorodecalin (20 area %); data as above, a trace amount of trifluorodecalin; *m/z* (EI^+) 192 (M^+, 76%), 172 (23, M^+-HF), unidentified products (68 area %) and tar (13%).

Propionitrile. *cis*-Decalin (**46**) (5.7 g, 42 mmol), elemental fluorine (208 mmol), and anhydrous propionitrile (140 cm^3) gave a pale brown crude product (9.0 g) which contained *cis*-9-fluorodecalin (**47**) (2.6 g, 50%, 78% conv.); data as above, difluorodecalin (8 area %); data as above, unsaturated decalin derivatives (7 area %) and unidentified products.

Formic acid. *cis*-Decalin (**46**) (3.0 g, 22 mmol), elemental fluorine (24 mmol), and formic acid (140 cm^3) gave a brown crude product (3.5 g) which contained *cis*-decalin (**46**) (98 area %), fluorodecalin (not *cis*-9-fluorodecalin) (1 area %); *m/z* (EI^+) 156 (M^+, 15%), 136 (52, M^+-HF), unsaturated decalin derivatives (1 area %); data as above and a trace amount of tar.

Sulfuric acid. *cis*-Decalin (**46**) (5.7 g, 42 mmol), elemental fluorine (208 mmol), and 98% sulfuric acid (140 cm^3) gave a brown crude product which contained *cis*-decalin (**46**) and tar (25%).

Trifluoroacetic acid. *cis*-Decalin (**46**) (5.7 g, 42 mmol), elemental fluorine (208 mmol), and trifluoroacetic acid (140 cm^3) gave a brown crude product (11.5 g) which contained *cis*-decalin (**46**) (31 area %), a trace amount of *cis*-9-fluorodecalin (**47**); data as above, difluorodecalin (1 area %); data as above, trifluorodecalin (2 area %); data as above, unsaturated decalin derivatives (51 area %); data as above, unidentified products (16 area %) and tar (33%).

Triflic acid-Freon 113 (1:1). *cis*-Decalin (**46**) (5.7 g, 42 mmol), elemental fluorine (208 mmol), Freon 113 (70 cm^3), and triflic acid (70 cm^3) gave a brown crude product (5.3 g) which contained a trace amount of *cis*-9-fluorodecalin (**47**); data as above, unsaturated decalin derivatives (49 area %); data as above, diunsaturated decalin derivatives (7 area %); *m/z* (EI^+) 134 (M^+, 100%), 119 (76), a trace amount of decalin dimer; *m/z* (EI^+) 274 (M^+, 33%), unidentified products (44 area %) and tar (28%).

Triflic acid-Freon 113 (1:19). *cis*-Decalin (**46**) (5.7 g, 42 mmol), elemental fluorine (208 mmol), anhydrous Freon 113 (133 cm^3), and triflic acid (7 cm^3) gave a black crude product (7.4 g) which contained *cis*-decalin (**46**) (20 area %), a trace

amount of *cis*-9-fluorodecalin (**47**); data as above, unsaturated decalin derivatives (69 area %); data as above, unidentified products (11 area %) and tar (28%).

Boron trifluoride-DCM (1:20). *cis*-Decalin (**46**) (2.6 g, 19 mmol), elemental fluorine (78 mmol), anhydrous DCM (112 g, 1 mol), and boron trifluoride etherate (9.3 g, 65 mmol) gave a brown crude product (4.8 g) which contained *cis*-decalin (**46**) and tar (9%).

Boron trifluoride-DCM (1:5). *cis*-Decalin (**46**) (2.7 g, 19 mmol), elemental fluorine (78 mmol), anhydrous DCM (90.0 g, 1 mol), and boron trifluoride etherate (30.0 g, 211 mmol) gave a brown crude product (4.9 g) which contained *cis*-decalin (**46**) and tar (8%).

α,α,α-Trifluoroethanol. *cis*-Decalin (**46**) (1.0 g, 7 mmol), elemental fluorine (18 mmol), and α,α,α-trifluoroethanol (65 cm^3) gave a pale yellow crude product (1.8 g) which contained *cis*-decalin (**46**) (39 area %), fluorodecalin (not *cis*-9-fluorodecalin) (5 area %); data as above, unsaturated decalin derivatives (6 area %); data as above and unidentified products (50 area %).

Freon 113. *cis*-Decalin (**46**) (5.7 g, 42 mmol), elemental fluorine (208 mmol), and Freon 113 (140 cm^3) gave a pale brown crude product (10.8 g) which contained *cis*-9-fluorodecalin (**47**) (0.4 g, 8%, 85% conv.); data as above, difluorodecalin (3 area %); data as above, tetrafluorodecalin (3 area %); *m/z* (EI^+) 210 (M^+, 8%), unsaturated decalin derivatives (7 area %); data as above, unidentified products (55 area %) and tar (15%).

Dichloromethane (substrate : fluorine = 1 : 5). *cis*-Decalin (**46**) (5.7 g, 42 mmol), elemental fluorine (208 mmol), and anhydrous dichloromethane (140 cm^3) gave a colourless crude product (6.0 g) which contained *cis*-decalin (**46**) (96 area %), a trace amount of *cis*-9-fluorodecalin (**47**); data as above, a trace amount of tetrachloroethane; *m/z* (EI^+) 166 (M^+, 17%), 83 (100, M^+-$CHCl_2$) and unidentified products (4 area %).

Dichloromethane (substrate : fluorine = 1 : 10). *cis*-Decalin (**46**) (2.9 g, 21 mmol), elemental fluorine (208 mmol), and anhydrous dichloromethane (140 cm^3) gave a yellow crude product (4.9 g) which contained *cis*-decalin (**46**) (89 area %), *cis*-9-fluorodecalin (**47**) (1 area %); data as above, a trace amount of tetrachloroethane; data as above and unidentified products (10 area %).

Nitromethane (substrate:fluorine = 1:5). *cis*-Decalin (**46**) (5.7 g, 42 mmol), elemental fluorine (208 mmol), and anhydrous nitromethane (140 cm^3) gave a yellow crude product (7.4 g) which contained *cis*-9-fluorodecalin (**47**) (2.1 g, 33%, 97% conv.); data as above, difluorodecalin (7 area %); data as above, trifluorodecalin (12 area %); data as above, tetrafluorodecalin (3 area %); data as above, unidentified products (60 area %) and tar (24%).

Acetonitrile-Freon 113 (1:4). *cis*-Decalin **(46)** (5.7 g, 42 mmol), elemental fluorine (208 mmol), anhydrous Freon 113 (112 cm^3), and anhydrous acetonitrile (28 cm^3) gave a pale brown crude product (13.5 g) which contained *cis*-9-fluorodecalin **(47)** (2.3 g, 56%, 63% conv.); data as above, difluorodecalin (10 area %); data as above, trifluorodecalin (1 area %); data as above, unsaturated decalin derivatives (6 area %); data as above and unidentified products.

Acetonitrile-Freon 113 (1:9). *cis*-Decalin **(46)** (2.2 g, 16 mmol), elemental fluorine (78 mmol), anhydrous Freon 113 (126 cm^3), and anhydrous acetonitrile (14 cm^3) gave a yellow crude product (5.2 g) which contained *cis*-9-fluorodecalin **(47)** (1.2 g, 52%, 92% conv.); data as above, difluorodecalin (3 area %); data as above, trifluorodecalin (3 area %); data as above, unsaturated decalin derivatives (2 area %); data as above and unidentified products.

Acetonitrile-Freon 113 (1:19). *cis*-Decalin **(46)** (5.7 g, 42 mmol), elemental fluorine (208 mmol), anhydrous Freon 113 (133 cm^3), and anhydrous acetonitrile (7 cm^3) gave a pale yellow crude product (8.8 g) which contained *cis*-9-fluorodecalin **(47)** (0.7 g, 27%, 40% conv.); data as above, difluorodecalin (1 area %); data as above, trifluorodecalin (1 area %); data as above and unidentified products.

Acetonitrile-dichloromethane (1:19). *cis*-Decalin **(46)** (5.7 g, 42 mmol), elemental fluorine (208 mmol), anhydrous dichloromethane (133 cm^3), and anhydrous acetonitrile (7 cm^3) gave a pale brown crude product (8.8 g) which contained *cis*-decalin **(46)** (98 area %) and unidentified products (2 area %).

Acetonitrile and 1,4-dinitrobenzene (2%). *cis*-Decalin **(46)** (5.7 g, 42 mmol), elemental fluorine (208 mmol), anhydrous acetonitrile (140 cm^3), and 1,4-dinitrobenzene (0.14 g, 0.8 mmol) gave a brown crude product (9.4 g) which contained *cis*-9-fluorodecalin **(47)** (3.3 g 60%, 83% conv.); data as above, difluorodecalin (5 area %); data as above, trifluorodecalin (2 area %); data as above, unsaturated decalin derivatives (13 area %) and unidentified products.

Acetonitrile and 1,4-dinitrobenzene (5%). *cis*-Decalin **(46)** (5.7 g, 42 mmol), elemental fluorine (208 mmol), anhydrous acetonitrile (140 cm^3), and 1,4-dinitrobenzene (0.35 g, 2 mmol) gave a brown crude product (7.0 g) which contained *cis*-9-fluorodecalin **(47)** (3.3 g, 65%, 77% conv.); data as above, difluorodecalin (5 area %); data as above, trifluorodecalin (6 area %); data as above, unsaturated decalin derivatives (8 area %), unidentified products and tar (1%).

Acetonitrile and 1,4-dinitrobenzene (8%). *cis*-Decalin **(46)** (5.7 g, 42 mmol), elemental fluorine (208 mmol), anhydrous acetonitrile (140 cm^3), and 1,4-dinitrobenzene (0.56 g, 3 mmol) gave a brown crude product (15.1 g) which contained *cis*-9-fluorodecalin **(47)** (3.7 g 66%, 85% conv.); data as above, difluorodecalin (5 area %); data as above, trifluorodecalin (5 area %); data as above, unsaturated decalin derivatives (13 area %), unidentified products and tar (1%).

Acetonitrile and anisole. Elemental fluorine (33 mmol), as a 10% (v/v) mixture with nitrogen, was passed through cooled (0°C), stirred acetonitrile (140 cm^3), after addition of all the fluorine, anisole (1.8 g, 16 mmol) was added to the fluorinated mixture and after 30 min the resulting mixture was worked up as above and gave a pale brown crude product mixture (7.5 g) which contained anisole (98 area %), 2-fluoroanisole (1 area %); δ_F(188 MHz) -137.67 (4.7 F, m) and 4-fluoroanisole (1 area %); δ_F(188 MHz) -126.53 (1.0 F, m).

6.2 Selective fluorination of hydrocarbon compounds using elemental fluorine

General procedure. Exactly as for the direct fluorination solvent survey until purification of the crude product mixture unless stated otherwise. The fluorination of cyclohexane **(36)** was performed with a cold trap (-78°C) between the outlet of the reaction vessel and the inlet of the soda lime tower. The contents of the trap were combined with the contents of the reaction vessel after the final nitrogen purge.

Fluorocyclohexane (37). As stated in the general procedure with the exception that the organic extract was evaporated using traditional distillation apparatus fitted with a vigereux column. Cyclohexane **(36)** (10.9 g, 130 mmol), elemental fluorine (65 mmol), and anhydrous acetonitrile (140 cm^3) gave a yellow crude product mixture (11.1 g) which contained fluorocyclohexane **(37)** (4.4 g, 63%, 53% conv.), difluorocyclohexane (1 area %); *m/z* (EI^+) 120 (M^+, 12%), 99 (10), 85 (55) and unidentified products. Purification of the crude product by preparative scale GC gave a sample of fluorocyclohexane as a colourless liquid; bp 101-103°C (lit.,[142] 62°C/180mmHg) (Found: M^+, 102.0845. $C_6H_{11}F$ requires: M^+, 102.0845); NMR spectrum 1; Mass spectrum 1; IR spectrum 1.

***cis*-9-Fluorodecalin (47).** See above.

***trans*-9-Fluorodecalin (49).** *trans*-Decalin **(48)** (3.0 g, 22 mmol), elemental fluorine (110 mmol), and anhydrous acetonitrile (140 cm^3) gave a yellow crude product (5.0 g) which contained *trans*-9-fluorodecalin **(49)** (1.3 g, 54%, 68% conv.) and a trace amount of difluorodecalin; data as above. Purification of the crude product by preparative scale GC gave an analytically pure sample of *trans*-9-fluorodecalin **(49)** as a colourless liquid; bp 197-198°C (Found: C, 76.8; H, 11.0. $C_{10}H_{17}F$ requires: C, 76.9; H, 11.0%); NMR spectrum no. 3[108]; Mass spectrum no. 3; IR spectrum no. 3.

***exo*- and *endo*-2-Fluoronorbornane (43A, B).** Norbornane **(41)** (4.9 g, 51 mmol), elemental fluorine (195 mmol), and anhydrous acetonitrile (140 cm^3) gave a reaction mixture which was poured into iced water (*ca.* 150 cm^3), neutralised ($NaHCO_3$) and filtered to remove the solid brown crude product (7.0 g) which contained *exo*- and *endo*-2-fluoronorbornane **(43A, B)** (1.4 g, 41%, 60% conv.) in the ratio of 5.3 : 1.0 respectively and unidentified products. Purification of the crude

product by preparative scale GC gave a sample of *exo*- and *endo*-2-fluoronorbornane **(43A, B)** as an isomeric mixture and as a white solid; mp 54-60°C (sealed tube) (Found: volatility prevented high resolution MS determination); NMR spectrum 6 (^{13}C of *exo*-isomer[111]); Mass spectrum 6; IR spectrum 6.

1-Fluoroadamantane (44). Adamantane **(39)** (4.0 g, 29 mmol), elemental fluorine (205 mmol), and anhydrous acetonitrile (140 cm^3) gave a pale brown crude product which contained 1-fluoroadamantane **(44)** and 2-fluoroadamantane; δ_F(188 MHz) -174.12 (d, $^2J_{HF}$ 51.1)[143]; *m/z* (EI$^+$) 154 (M^+, 75%), 111 (19) in the ratio of 5.5 : 1 respectively and unidentified products. Purification of the mixture by column chromatography on silica gel using 6:1 cyclohexane-DCM as the eluent gave 1-fluoroadamantane **(44)** (2.1 g, 65%, 70% conv.) as a white solid; mp 256-258°C (lit.,[127] 257-259°C); R_f 0.52 (Found C, 77.8; H, 9.9. $C_{10}H_{15}F$ requires: C, 77.9; H, 9.8%); NMR spectrum 7(^{19}F[144], ^{13}C[145]); Mass spectrum 7; IR spectrum 7.

1-Fluoro-2-methylheptane (51A) and 1-fluoro-6-methylheptane (51B). 2-Methylheptane **(50)** (8.2 g, 72 mmol), elemental fluorine (72 mmol), and anhydrous acetonitrile (140 cm^3) gave a pale yellow crude product mixture (9.3 g) which contained at least four isomers of fluoromethylheptane (65 area %) including 1-fluoro-2-methylheptane **(51A)** (1.1 g, 15%, 81% conv.) and 1-fluoro-6-methylheptane **(51B)** (0.7 g, 9%, 81% conv.) and unidentified products. Purification of the crude product by preparative scale GC gave an analytically pure sample of 1-fluoro-2-methylheptane **(51A)** and 1-fluoro-6-methylheptane **(51B)** as an isomeric mixture and as a colourless liquid; (Found: C, 72.4; H, 13.3. $C_8H_{17}F$ requires: C, 72.7; H, 13.0%); NMR spectrum 8; Mass spectrum 8; IR spectrum 8.

2-, 3-, 4-, and 5-Fluorodecane (53A-D). Decane **(52)** (11.1 g, 78 mmol), elemental fluorine (78 mmol), and anhydrous acetonitrile (140 cm^3) gave a brown crude product mixture (12.1 g) which contained 2-, 3-, 4-, and 5-fluorodecane **(53A-D)** (4.8 g, 63%, 61% conv.) in the ratio of 1.0 : 1.1 : 1.2 : 2.6 not necessarily respectively, 1-fluorodecane **(53E)** in the ratio of 0.4 relative to other isomers; δ_F(188 MHz) -217.56 (m) and (> 25) unidentified products. Purification of the crude product by preparative scale GC gave an analytically pure sample of 2-, 3-, 4-, and 5-fluorodecane **(53A-D)** as an isomeric mixture and as a colourless liquid (Found: C, 74.7; H, 13.4. $C_{10}H_{21}F$ requires: C, 75.0; H, 13.2%); NMR spectrum 9; Mass spectrum 9; IR spectrum 9.

3β-Acetoxy-5α-androstan-18-one (55). A solution containing epiandrostanone **(54)** (1.0 g, 3 mmol), acetic anhydride (0.6 g, 6 mmol), and 4-dimethylaminopyridine (0.2 g, 1 mmol) in DCM (90 cm^3) was stirred at room temperature and after 2 h the reaction mixture was poured into water, neutralised ($NaHCO_3$) and extracted with DCM (3 x 20 cm^3). The combined, dried ($MgSO_4$) organic extracts were evaporated under reduced pressure to leave 3-β-acetoxy-5α-

androstan-17-one (**55**) (1.1 g, 96%, 100% conv.) as a white solid; mp 105-107°C (lit.,[146] 103-104°C) (Found C, 75.9; H, 10.0. $C_{21}H_{32}O_3$ requires: C, 75.9; H, 9.7%); NMR spectrum 10 (^{13}C[147]); Mass spectrum 10; IR spectrum 10.

3β-Acetoxy-5α-fluoroandrostan-18-one (56A-C). 3β-Acetoxy-5α-androstan-18-one (**55**) (3.0 g, 9 mmol), elemental fluorine (27 mmol), and anhydrous acetonitrile (140 cm^3) gave a pale yellow solid (3.1 g) which contained 3β-acetoxy-5α-androstan-18-one (**55**) (59 area %), three isomers of acetoxyfluoroandrostanone (**56A-C**) in the ratio of 1.1 : 1.0 : 1.4 (31 area %); δ_F(188 MHz) -162.39 (t, $^3J_{HF}$ 38.9, 3-F or 5-F), 164.09 (ddd, $^3J_{HF}$ 15.4, $^3J_{HF}$ 31.0, $^3J_{HF}$ 45.1, 9-F or 14-F), 179.70 (ddd, $^3J_{HF}$ 11.1, $^3J_{HF}$ 27.8, $^3J_{HF}$ 41.6, 9-F or 14-F); *m/z* (EI^+) 350 (M^+, 11%), 330 (21, M^+-HF) (Found: M^+, 350.2260. $C_{21}H_{31}FO_3$ requires: M^+, 350.2257), a trace amount of unsaturated acetoxyandrostanone; *m/z* (EI^+) 330 (M^+, 13%), 315 (7) and a trace amount of difluoroacetoxyandrostanone; *m/z* (EI^+) 368 (M^+, 5%), 348 (4, M^+-HF). Purification by column chromatography, recrystallisation and HPLC proved unsuccessful.

6.3 Selective fluorination of hydrocarbon compounds using Selectfluor™

General procedure. A mixture consisting of the substrate, Selectfluor™, and anhydrous acetonitrile was stirred and heated (82°C) then poured into water (70 cm^3), neutralised ($NaHCO_3$) and extracted with DCM (3 x 40 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated to leave the crude product mixture which was analysed as for the direct fluorination reactions.

Fluorocyclohexane (37). Cyclohexane (**36**) (3.0 g, 36 mmol), Selectfluor™ (13.9 g, 39 mmol), and anhydrous acetonitrile (130 cm^3) gave, after 26 h of heating, a colourless product mixture (8.0 g) which contained fluorocyclohexane (**37**) (0.8 g, 22%, 100% conv.); data as above and trace amounts of unidentified products.

***trans*-1- and 2-Fluorodecalin (63A-D).** *trans*-Decalin (**48**) (5.4 g, 39 mmol), Selectfluor™ (24.9 g, 70 mmol), and anhydrous acetonitrile (250 cm^3) gave, after 3.5 h of heating, a pale brown crude product mixture (8.7 g) which contained *trans*-1-fluoro$_{(eq)}$decalin (**63A**), *trans*-1-fluoro$_{(ax)}$decalin (**63B**), *trans*-2-fluoro$_{(eq)}$decalin (**63C**) and *trans*-2-fluoro$_{(ax)}$decalin (**63D**) (2.0 g, 80%, 41% conv.) in the ratio of 1.1 : 1.0 : 1.4 : 2.2 respectively and unidentified products. Purification of the crude product by preparative scale GC gave an analytically pure sample of *trans*-1-fluoro$_{(eq)}$decalin (**63A**), *trans*-1-fluoro$_{(ax)}$decalin (**63B**), *trans*-2-fluoro$_{(eq)}$decalin (**63C**), and *trans*-2-fluoro$_{(ax)}$decalin (**63D**) as an isomeric mixture and as a colourless liquid (Found: C, 77.0; H, 11.1. $C_{10}H_{17}F$ requires: C, 76.9; H, 11.0%); NMR spectrum 4; Mass spectrum 4; IR spectrum 4.

Since the interpretation of NMR spectra no. 4 was not straight forward what follows below is a description of the procedure which was used to assign (some of) the peaks in the spectra and, therefore, determine the identity of the products.

The ^{13}C NMR spectrum of the isomeric mixture contains doublet peaks which are the result of carbon-fluorine couplings and it is not possible to differentiate between such doublets and two singlets (which are relatively close together) using the ^{13}C NMR spectrum of the mixture. Consequently, two DEPT spectra of the mixture were acquired on two spectrometers that are of different fields and the spectra were interpreted as detailed below.

Both spectra were printed using exactly the same scale and then the distance between corresponding peaks in each spectrum was compared. Doublet peaks appear further apart in the spectrum which was determined using the lower field machine and, therefore, doublets can be distinguished easily from two singlets.

The two DEPT spectra were used to ascertain that the mixture contained eight types of tertiary C-H bonds, twenty eight CH_2-types of carbon and four CHF.

The CHF proton in each isomer was readily identified in the ^{1}H NMR spectrum of the mixture. Each CHF proton in each isomer exists in a unique environment and, therefore, displays a unique splitting pattern.

Two of the four ^{1}H NMR CHF splitting patterns can be assigned unambiguously to two of the four monofluorinated isomers (this was described in Chapter 2, Section 2.5.2; page 64). Isomers which could be assigned using this method were *trans*-1-fluoro$_{(eq)}$decalin **(63A)** and *trans*-2-fluoro$_{(eq)}$decalin **(63C)**. Due to ambiguous splitting patterns, the remaining two isomers, *trans*-1-fluoro$_{(ax)}$decalin **(63B)** and *trans*-2-fluoro$_{(ax)}$decalin **(63D)**, could not be assigned to the remaining two proton signals using this method.

An HSQCTOCSY NMR experiment (Figure 5) was used to identify (most of) the ^{13}C NMR signals and one CHF signal in the ^{1}H NMR spectrum which represent each molecule.

The relative intensity of each CHF peak in the ^{13}C NMR spectrum was used to match each group of ^{13}C NMR signals to a CHF proton in the ^{1}H NMR spectrum.

The two isomers which remained unassigned were correlated with a group of ^{13}C NMR signals (and one ^{1}H NMR CHF signal) by considering the splitting patterns which the group of ^{13}C NMR signals display.

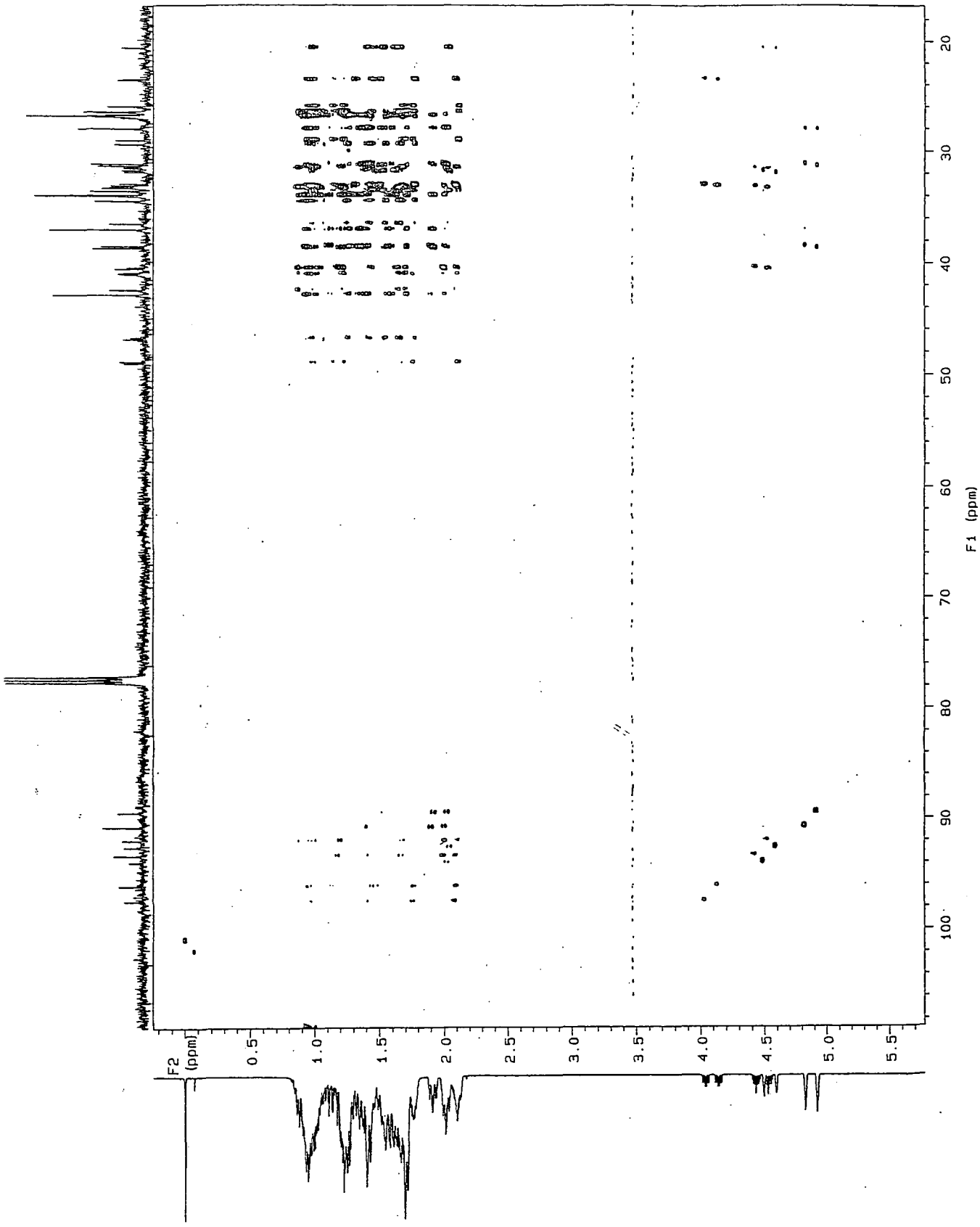
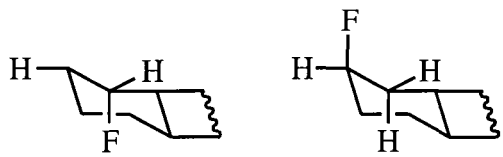

F2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
F1 (ppm)
20
30
40
50
60
70
80
90
100

Figure 5

The two remaining unassigned isomers are shown in Scheme 6.1.



(63B) **(63D)**

Scheme 6.1

63B contains one CH and one CH_2 type of carbon which are both two bonds away from the fluorine atom. The group of ^{13}C NMR signals which represent this isomer should, therefore, contain one CH and one CH_2 type of carbon which is split by a 15Hz coupling constant. In contrast, the group of ^{13}C NMR signals which represent **63D** should contain two CH_2 signals which display a two bond C-F coupling pattern.

Both groups of ^{13}C NMR signals display the required characteristics and therefore the complete assignment of the spectra was possible.

***cis*-1- and 2-Fluorodecalin (64A-D).** *cis*-Decalin (**46**) (3.0 g, 22 mmol), Selectfluor^{TM} (13.9 g, 39 mmol), and anhydrous acetonitrile (150 cm^3) gave, after 1.5 h of heating, a pale brown crude product mixture (3.2 g) which contained *cis*-1-fluoro$_{(eq)}$decalin (**64A**), *cis*-1-fluoro$_{(ax)}$decalin (**64B**), *cis*-2-fluoro$_{(eq)}$decalin (**64C**), and *cis*-2-fluoro$_{(ax)}$decalin (**64D**) (1.2 g, 58%, 61%) in the ratio of 1.0 : 1.3 : 1.4 : 1.6 not necassarily respectively and unidentified products. Purification of the crude product by preparative scale GC gave an analytically pure sample of *cis*-1-fluoro$_{(eq)}$decalin (**64A**), *cis*-1-fluoro$_{(ax)}$decalin (**64B**), *cis*-2-fluoro$_{(eq)}$decalin (**64C**), and *cis*-2-fluoro$_{(ax)}$decalin (**64D**) as an isomeric mixture and as a colourless liquid (Found: C, 77.0; H, 11.1. $C_{10}H_{17}F$ requires: C, 76.9; H, 11.0%); NMR spectrum 5 (determied at -57°C); Mass spectrum 5; IR spectrum 5.

1-Fluoroadamantane (44). Adamantane (**39**) (1.0 g, 7 mmol), Selectfluor^{TM} (4.7 g, 13 mmol), and anhydrous acetonitrile (100 cm^3) gave, after 3 h of heating, a pale brown crude product mixture (1.5 g) which contained 1-fluoroadamantane (**44**) (43 area %) and 2-fluoroadamantane; data as above, in the ratio of 5.5 : 1 respectively, adamantanol (4 area %); *m/z* (EI^+) 152 (M^+, 20%), 95 (100), N-(adamantyl)acetamide (1 area %); *m/z* (EI^+) 193 (M^+, 43%), 136 (53) and unidentified products. Purification of the mixture by column chromatography on silica gel using 6:1 cyclohexane-DCM as the eluent gave 1-fluoroadamantane (**44**) (0.5 g, 68%, 73% conv.) as a white solid; data as above.

2-, 3-, 4-, and 5-Fluorodecane (53A-D). Decane **(52)** (7.8 g, 55 mmol), Selectfluor^{TM} (21.4 g, 61 mmol), and anhydrous acetonitrile (210 cm^3) gave, after 18 h of heating, a pale brown product mixture (10.8 g) which contained 2-, 3-, 4-, and 5-fluorodecane **(53A-D)** (4.3 g, 58%, 84% conv.) in the ratio of 2.4 : 1.3 : 1.0 : 1.1 not necassarily respectively; data as above and (> 25) unidentified products.

6.4 Attempted fluorination of decane (52) using commercial fluorinating reagents

General procedure. Exactly as for selective fluorination reactions using Selectfluor^{TM} except hexane was used to extract the products.

NFSI (3.5 d). Decane **(52)** (4.0 g, 28 mmol), NFSI (9.8 g, 31 mmol), and anhydrous acetonitrile (80 cm^3) gave, after 3.5 d of heating, a colourless crude product (5.5 g) which contained 2-, 3-, 4-, and 5-fluorodecane **(53A-D)** (0.5 g, 49%, 21% conv.) in the ratio of 1.3 : 1.0 : 1.0 : 1.1 not necassarily respectively; data as above and unidentified products.

NFPY (3.5 d). Decane **(52)** (5.6 g, 39 mmol), NFPY (8.0 g, 43 mmol), and anhydrous acetonitrile (80 cm^3) gave, after 3.5 d of heating, a yellow crude product which contained decane **(52)** only.

Xenon difluoride (16 h). Decane **(52)** (6.0 g, 42 mmol), xenon difluoride (7.9 g, 46 mmol), and anhydrous acetonitrile (80 cm^3) gave, after 16 h of heating, a colourless product mixture (5.5 g) which contained 2-, 3-, 4-, and 5-fluorodecane **(53A-D)** (1.8 g, 47%, 57% conv.) in the ratio of 1.5 : 1.0 : 1.3 : 1.6 not necassarily respectively; data as above, 1-fluorodecane **(53E)** (in the ratio of 0.5 relative to above); δ_F (376MHz) 218.90 (m) and unidentified products.

Chapter 7: Experimental to Chapter 3

7.1 Preparations of amide compounds using Selectfluor™

General procedure. Exactly as for selective fluorination reactions using Selectfluor™.

N-(1-Adamantyl)acetamide (65). Adamantane (**39**) (2.0 g, 15 mmol), Selectfluor™ (13.5 g, 38 mmol), and anhydrous acetonitrile (120 cm^3) gave, after 4.5 d of heating, a brown product mixture (2.3 g) which contained 1-fluoroadamantane (**44**) (10 area %); data as above, difluoroadamantane (2 area %); *m/z* (EI^+) 172 (M^+, 48%), 152 (77, M^+-HF), N-(1-adamantyl)acetamide (**65**) (51 area %), N-(2-adamantyl)acetamide (13 area %); *m/z* (EI^+) 193 (M^+, 50%), 178 (10, M^+-CH_3), 150 (16, M^+-$COCH_3$) and unidentified products. Purification of the mixture by column chromatography on silica gel using 1:1 DCM-methanol as the eluent gave adamantane (0.1 g, 7%) N-(1-adamantyl)acetamide (**65**) (0.7 g, 25%, 93% conv.) as a white solid; mp 150-151°C (lit.,[148] 150-151°C); R_f 0.43 (Found C, 74.3; H, 10.0; N, 7.1. $C_{12}H_{19}NO$ requires: C, 74.6; H, 9.9; N, 7.3%); NMR spectrum 11 (^{13}C[149]); Mass spectrum 11; IR spectrum 11.

N-(1-Adamantyl)acetamide (65) - Sampling reaction. Adamantane (**39**) (1.5 g, 11 mmol), Selectfluor™ (9.7 g, 28 mmol), and anhydrous acetonitrile (100 cm^3) gave, after 6.5 d of heating, a brown product mixture (1.8 g) which contained adamantane (**39**) (1 area %), 1-fluoroadamantane (**44**) (3 area %); data as above, at least three isomers of difluoroadamantane (3 area %); data as above, adamantanol (2 area %); data as above, dihydroxyadamantane (1 area %); *m/z* (EI^+) 168 (M^+, 20%), 135 (100, M^+-H_2O), N-(1-adamantyl)acetamide (**65**) (55 area %); data as above, N-(2-adamantyl)acetamide (7 area %); *m/z* (EI^+) 193 (M^+, 50%), 178 (10, M^+-CH_3), 150 (16, M^+-$COCH_3$), at least four isomers of fluorinated N-(adamantyl)acetamide (11 area %); *m/z* (EI^+) 211 (M^+, 53%), 193 (16, M^+-HF) and unidentified products (17 area %).

N-(1-Adamantyl)propylamide (66). Adamantane (**39**) (2.5 g, 18 mmol), Selectfluor™ (11.7 g, 32 mmol), and anhydrous propionitrile (100 cm^3) gave, after 3 d of heating, a yellow crude product mixture (3.2 g) which was purified by column chromatography on silica gel using chloroform as the eluent gave N-(1-adamantyl)ethylamide (**66**) (2.4 g, 65%, 100% conv.) as a white solid; mp 103-105°C (lit.,[150] 104.2°C); R_f 0.35 (Found C, 75.2; H, 10.3; N, 6.9. $C_{13}H_{21}NO$ requires: C, 75.3; H, 10.2; N, 6.8%); NMR spectrum 12; Mass spectrum 12; IR spectrum 12.

7.2 Solvent survey

General procedure. A mixture consisting of the substrate, Selectfluor™ and the solvent was stirred and heated (82°C) then poured into water (70 cm^3), neutralised ($NaHCO_3$) and extracted with DCM (3 x 50 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to leave the crude product mixture which was analysed as for the direct fluorination reactions.

DCM. Adamantane (**39**) (1.5 g, 11 mmol), Selectfluor™ (4.8 g, 13 mmol), and anhydrous DCM (90 cm^3) gave, after 24 h of heating (45°C), a yellow crude product which contained adamantane (**39**) only.

DCM and trifluoroacetic acid. Adamantane (**39**) (1.5 g, 11 mmol), Selectfluor™ (4.8 g, 13 mmol), trifluoroacetic acid (5 cm^3), and anhydrous DCM (90 cm^3) gave, after 24 h of heating (45°C), a yellow crude product which contained adamantane (**39**) only.

Nitromethane. Adamantane (**39**) (1.5 g, 11 mmol), Selectfluor™ (4.8 g, 13 mmol), and anhydrous nitromethane (90 cm^3) gave, after 24 h of heating (55°C), a yellow crude product which contained adamantane (1 area %), fluoroadamantane (1 area %); data as above, hydroxyadamantane (17 area %); *m/z* (EI^+) 152 (M^+, 20%), 95 (100), two isomers of N-(adamantyl)propylamide (34 area %); data as above and unidentified products (48 area %).

Nitroethane (4 h). *cis*-Decalin (**46**) (5.0 g, 36 mmol), Selectfluor™ (14.1 g, 40 mmol), and anhydrous nitroethane (75 cm^3) gave, after 4 h of heating (82°C), a yellow product which contained *cis*-decalin (**46**) only.

Nitroethane (48 h). *cis*-Decalin (**46**) (5.0 g, 36 mmol), Selectfluor™ (14.1 g, 40 mmol) and anhydrous nitroethane (75 cm^3) gave, after 48 h of heating (82°C), a yellow product which contained *cis*-decalin (**46**) only.

7.3 Amidation of adamantane using elemental fluorine

General procedure. As for fluorination of hydrocarbon compounds using elemental fluorine except boron trifluoride etherate or tetrafluoroboric acid etherate (54% by weight) was added to the reaction mixture prior to the addition of fluorine.

Boron trifluoride etherate (1 molar equiv.). Adamantane (**39**) (1.5 g, 11 mmol), elemental fluorine (44 mmol), boron trifluoride etherate (1.6 g, 11 mmol), and anhydrous acetonitrile (120 cm^3) gave a crude product mixture (1.8 g) which contained adamantane (**39**) (35 area %), N-(1-adamantyl)acetamide (**65**) (55 area %); data as above, N-(2-adamantyl)acetamide (9 area %); data as above and unidentified products (1 area %).

Boron trifluoride etherate (0.1 molar equiv.). Adamantane (**39**) (1.5 g, 11 mmol), elemental fluorine (44 mmol), boron trifluoride etherate (0.2 g, 1 mmol), and

anhydrous acetonitrile (120 cm^3) gave a crude product mixture (2.1 g) which contained adamantane (**39**) (24 area %), N-(1-adamantyl)acetamide (**65**) (11 area %); data as above, 1-fluoroadamantane (**44**) (49 area %); data as above and unidentified products (16 area %).

Tetrafluoroboric acid etherate (1 molar equiv.). Adamantane (**39**) (1.5 g, 11 mmol), elemental fluorine (44 mmol), tetrafluoroboric acid etherate (1.9 g, 11 mmol), and anhydrous acetonitrile (120 cm^3) gave a crude product mixture (2.2 g) which contained adamantane (**39**) (34 area %), N-(1-adamantyl)acetamide (**65**) (55 area %); data as above, N-(2-adamantyl)acetamide (8 area %); data as above and unidentified products (3 area %).

Tetrafluoroboric acid etherate (0.1 molar equiv.). Adamantane (**39**) (1.5 g, 11 mmol), elemental fluorine (44 mmol), tetrafluoroboric acid etherate (0.2 g, 1 mmol), and anhydrous acetonitrile (120 cm^3) gave a crude product mixture (2.3 g) which contained adamantane (**39**) (45 area %), N-(1-adamantyl)acetamide (**65**) (7 area %); data as above, 1-fluoroadamantane (**44**) (36 area %); data as above and unidentified products (12 area %).

7.4 Selective amidation of hydrocarbon compounds using elemental fluorine

General procedure. As for selective fluorination reactions using elemental fluorine except boron trifluoride etherate was added to the reaction mixture prior to the addition of elemental fluorine. After the final nitrogen purge, a sample of the mixture was subject to ^{19}F NMR spectroscopy and if fluoroalkane was observed the mixture was heated for 15 min.

N-(Cyclohexyl)acetamide (67). Cyclohexane (**36**) (9.8 g, 117 mmol), elemental fluorine (59 mmol), boron trifluoride etherate (16.6 g, 117 mmol), and anhydrous acetonitrile (120 cm^3) gave, after heating (65°C) and the work-up as detailed above, a crude product mixture which was distilled to give cyclohexane (**36**) (4.6 g, 55 mmol); bp 67°C. The brown solid which remained gave, after recrystallisation, N-(cyclohexyl)acetamide (**67**) (4.5 g, 51%, 53% conv.) as a white solid; mp 104-105°C (from acetonitrile) (lit.,[151] 104-105°C) (Found C, 68.1; H, 10.7; N, 9.9. $C_8H_{15}NO$ requires: C, 68.1; H, 10.7; N, 9.9%); NMR spectrum 13; Mass spectrum 13; IR spectrum 13.

N-(*trans*-9-Decalyl)acetamide (68) from *cis*-decalin (46). *cis*-Decalin (**46**) (2.2 g, 16 mmol), elemental fluorine (65 mmol), boron trifluoride etherate (2.3 g, 16 mmol), and anhydrous acetonitrile (120 cm^3) gave, after heating (82°C) and the work-up as detailed above, a crude product mixture which was distilled to give decalin (**46**) (0.7 g, 5 mmol); bp 55°C/10mmHg. The brown solid which remained gave, after recrystallisation, N-(*trans*-9-decalyl)acetamide (**68**) (0.8 g, 49%, 67% conv.) as a

white solid; mp 183-184°C (from acetonitrile) (lit.,[152] 183°C) (Found C, 73.6; H, 10.9; N, 7.3. $C_{12}H_{21}NO$ requires: C, 73.8; H, 10.9; N, 7.2%); NMR spectrum 14; Mass spectrum 14; IR spectrum 14.

N-(*trans*-9-Decalyl)acetamide (68) from *trans*-decalin (48). *trans*-Decalin (**48**) (3.0 g, 22 mmol), elemental fluorine (44 mmol), boron trifluoride etherate (3.1 g, 22 mmol), and anhydrous acetonitrile (120 cm^3) gave, after heating (82°C) and the work-up as detailed above, a crude product mixture which was distilled to give decalin (**48**) (1.5 g, 11 mmol); bp 50°C/8mmHg. The brown solid which remained gave, after recrystallisation, N-(*trans*-9-decalyl)acetamide (**68**) (1.0 g, 45%, 49% conv.) as a white solid; data as above.

N-(*exo*-2-Norbornyl)acetamide (69). Norbornane (**41**) (2.4 g, 25 mmol), elemental fluorine (59 mmol), boron trifluoride etherate (3.6 g, 25 mmol), and anhydrous acetonitrile (120 cm^3) gave a reaction mixture which was poured into water, neutralised ($NaHCO_3$) and filtered to remove norbornane (**41**) (1.0 g, 10 mmol). The liquid which remained was worked up as above and gave, after recrystallisation, N-(*exo*-2-norbornyl)acetamide (**69**) (1.0 g, 45%, 60% conv.) as a white solid; 141-142°C (from acetonitrile) (lit.,[153] 141-142°C) (Found C, 70.2; H, 10.2; N, 9.3. $C_9H_{15}NO$ requires: C, 70.5; H, 9.9; N, 9.2%); NMR spectrum 15; Mass spectrum 15; IR spectrum 15.

N-(1-Adamantyl)acetamide (65). Adamantane (**39**) (1.5 g, 11 mmol), elemental fluorine (44 mmol), boron trifluoride etherate (1.6 g, 11 mmol), and anhydrous acetonitrile (120 cm^3) gave, after purification by column chromatography on silica gel using 1:1 DCM-methanol as the eluent, adamantane (**39**) (0.4 g, 3 mmol) and N-(1-adamantyl)acetamide (**65**) (0.9 g, 54%, 74% conv.) as a white solid; data as above.

7.5 Selective functionalisation of adamantane using elemental fluorine

General procedure. Fluorination was carried out as above and then the mixture was poured into water (50 cm^3) and extracted using DCM (3 x 40 cm^3). The combined organic extracts were washed (multiple times) with water, dried ($MgSO_4$) and evaporated to a volume of *ca.* 50 cm^3. Boron trifluoride etherate was added to the stirred mixture and after 5 min., the nucleophile was added. Stirring was continued for 15 min. and after this time the mixture was worked up as usual to give a crude product. Pure adamantane derivatives were isolated using either column chromatography or recrystallisation.

1-Aminoadamantane (70). Adamantane (**39**) (7.1 g, 52 mmol), elemental fluorine (208 mmol), boron trifluoride etherate (29.5 g, 208 mmol), $ammonia_{(aq)}$ (20 cm^3), and anhydrous acetonitrile (120 cm^3) gave, after purification by recrystallistion

1-aminoadamantane **(70)** (4.0 g, 62%, 70% conv.) as a white solid; mp 189-191°C (sealed tube) (lit.,[154] 189-191°C) (Found M^+, 151.1371 $C_{10}H_{17}N$ requires: M^+, 151.1361); NMR spectrum 16 (^{13}C[155]); Mass spectrum 16; IR spectrum 16.

1-Hydroxyadamantane (71). Adamantane **(39)** (7.1 g, 52 mmol), elemental fluorine (208 mmol), boron trifluoride etherate (29.5 g, 208 mmol), water (20 cm^3), and anhydrous acetonitrile (120 cm^3) gave, after purification by column chromatography on silica gel using 1:1 diethyl ether-hexane as the eluent, 1-hydroxyadamantane **(71)** (3.7 g, 66%, 70% conv.) as a white solid; mp 248-249°C (sealed tube); R_f = 0.46 (Found M^+, 152.1196 $C_{10}H_{16}O$ requires: M^+, 152.1201); NMR spectrum 17 (^{13}C[155]); Mass spectrum 17; IR spectrum 17.

1-Ethoxyadamantane (72). Adamantane **(39)** (7.1 g, 52 mmol), elemental fluorine (208 mmol), boron trifluoride etherate (29.5 g, 208 mmol), anhydrous ethanol (40 cm^3), and anhydrous acetonitrile (120 cm^3) gave, after purification by column chromatography on silica gel using DCM as the eluent, 1-ethoxyadamantane **(72)** (2.8 g, 51%, 70% conv.) as a colourless oil; bp 110-111°C (lit.,[156] 110-111°C) R_f = 0.52 (Found C, 79.8; H, 11.3. $C_{12}H_{20}O$ requires: C, 79.9; H, 11.2%); NMR spectrum 18(^1H[156]); Mass spectrum 18; IR spectrum 18.

Chapter 8: Experimental to Chapter 4

8.1 Fluorination of ester substrates using elemental fluorine

General procedure. Exactly as for direct fluorination of hydrocarbon compounds.

Methyl 3- and 4-fluorovalerate (74A, B) (0°C). Methyl valerate (**73**) (5.1 g, 44 mmol), elemental fluorine (220 mmol), and anhydrous acetonitrile (140 cm^3) gave a brown crude product mixture (10.0 g) which contained methyl 3- and 4-fluorovalerate (**74A, B**) (0.9 g, 21%, 66% conv.) in the ratio of 1.0 : 3.2 respectively, (> 25) unidentified products and tar (7%). Purification of the crude product by preparative scale GC gave an isomeric mixture of methyl 3- and 4-fluorovalerate (**74A, B**) as a colourless liquid; (Found: M^++NH_4, 152.1092. $C_6H_{11}FO_2$ requires: M^++NH_4, 152.1087 -methyl valerate (<3%) present in the purified sample-); methyl 3-fluorovalerate NMR spectrum 19; methyl 4-fluorovalerate NMR spectrum 20; methyl 3- and 4-fluorovalerate Mass spectrum 19; IR spectrum 19.

Methyl 3-, 4-, 5-, and 6-fluoroenanthate (76A-D). Methyl enanthate (**75**) (4.4 g, 30 mmol), elemental fluorine (91 mmol), and anhydrous acetonitrile (140 cm^3) gave a brown crude product mixture (7.3 g) which contained methyl 3-, 4-, 5-, and 6-fluoroenanthate (**76A-D**) (2.1 g, 68%, 64% conv.); in the ratio of 1.0 : 3.5 : 6.4 : 5.6 respectively; data as below, a trace amount of methyl 7-fluoroenanthate; δ_F(188 MHz) -217.23 (m) and (> 20) unidenitified products.

Attempted fluorination of dimethyl glutarate (77). Dimethyl glutarate (**77**) (2.4 g, 15 mmol), elemental fluorine (53 mmol) and anhydrous acetonitrile (140 cm^3) gave a yellow crude product mixture (3.6 g) which contained dimethyl glutarate (**77**) (99 area %) and unidentified products (1 area %).
Repetition of this reaction with 7 equivalents of fluorine gave a similar result.

Dimethyl 3- and 4-fluoropimelate (79A, B). Dimethyl pimelate (**78**) (2.9 g, 11 mmol), elemental fluorine (78 mmol), and anhydrous acetonitrile (140 cm^3) gave a pale yellow crude product mixture (6.5 g) which contained dimethyl 3- and 4-fluoropimelate (**79A, B**) (1.2 g, 54%, 98% conv.) in the ratio of 1.0 : 1.7 respectively and (> 20) unidentified products. Purification of the mixture by column chromatography on silica gel using 4:1 petroleum ether-ethyl acetate as the eluent gave dimethyl 3- and 4-fluoropimelate (**79A, B**) as an isomeric mixture and as a colourless oil; R_f 0.64 (Found: C, 52.5; H, 7.5. $C_9H_{15}FO_4$ requires: C, 52.4; H, 7.3%); NMR spectrum 22; Mass spectrum 21; IR spectrum 21.

8.2 Fluorination of alkyl halide substrates using elemental fluorine

Attempted fluorination of 1-iodohexane (80). 1-Iodohexane (**80**) (8.0 g, 38 mmol), elemental fluorine (38 mmol), and anhydrous acetonitrile (140 cm^3) gave a red-purple reaction mixture which was decolourised using aqueous sodium metabisulfite and then worked up as above to give a yellow crude product mixture (7.6 g) which contained 1-iodohexane (**80**) (85 area %) and (> 20) unidentified products.

Repetition of this reaction gave a similar result.

Attempted fluorination 1-bromohexane (81). 1-Bromohexane (**81**) (5.0 g, 30 mmol), elemental fluorine (60 mmol), and anhydrous acetonitrile (140 cm^3) gave an orange reaction mixture which was decolourised using aqueous sodium metabisulfite and then worked up as above to give a yellow crude product mixture (6.2 g) which contained 1-bromohexane (**81**) (56 area %) and (> 20) unidentified products.

Repetition of this reaction gave a similar result.

1-Chloro-4-fluorohexane and 1-chloro-5-fluorohexane (84A, B). 1-Chlorohexane (**83**) (8.4 g, 69 mmol), elemental fluorine (208 mmol), and anhydrous acetonitrile (140 cm^3) gave a dark yellow crude product mixture (9.0 g) which contained 1-chloro-3-, 4- and 5-fluorohexane (**84A, B, C**) (1.5 g, 22%, 72% conv.) in the ratio of 1.0 : 1.8 : 1.9 respectively; data as below, a small amount of 1-chloro-6-fluorohexane; δ_F(188 MHz) -217.49 (m), (> 20) unidentified products and tar (10%).

8.3 Fluorination of ester substrates using Selectfluor™

General procedure. Exactly as for fluorination of hydrocarbon compounds using Selectfluor™.

Methyl 3- and 4-fluorovalerate (74A, B). Methyl valerate (**73**) (4.0 g, 34 mmol), Selectfluor™ (13.4 g, 38 mmol), and anhydrous acetonitrile (130 cm^3) gave, after 16 h of heating, a colourless product mixture (10.1 g) which contained methyl 3- and 4-fluorovalerate (**74A, B**) (1.3 g, 64%, 45% conv.) in the ratio of 1.0 : 1.2 respectively; data as above and (> 10) unidentified products.

Methyl 3-, 4-, 5-, and 6-fluoroenanthate (76A-D). Methyl enanthate (**75**) (4.0 g, 28 mmol), Selectfluor™ (13.6 g, 31 mmol), and anhydrous acetonitrile (140 cm^3) gave, after 16 h of heating, a yellow product mixture (4.7 g) which contained methyl 3-, 4-, 5- and 6-fluoroenanthate (**76A-D**) (1.2 g, 48%, 57% conv.) in the ratio of 1.0 : 1.3 : 1.3 : 3.7 respectively, methyl enanthate acetamide (4 area %); *m/z* (CI, NH_3) 219 (M^++18, 12%) and (> 10) unidentified products. Purification of the crude product by preparative scale GC gave an analytically pure sample of methyl 3-, 4-, 5- and 6-fluoroenanthate (**76A-D**) as an isomeric mixture and as a colourless liquid

(Found C, 59.1; H, 9.3. $C_8H_{15}O_2F$ requires: C, 59.2; H, 9.3%); NMR spectrum 21; Mass spectrum 20; IR spectrum 20.

Attempted fluorination of dimethyl glutarate (77). Dimethyl glutarate (**77**) (5.0 g, 31 mmol), Selectfluor^{TM} (12.2 g, 34 mmol), and anhydrous acetonitrile (120 cm^3) gave, after 7 d of heating, a yellow crude product mixture (5.2 g) which contained dimethyl glutarate (**78**) (98 area %) and unidentified products (2 area %).

Attempted fluorination of dimethyl pimelate (78). Dimethyl pimelate (**78**) (5.0 g, 27 mmol), Selectfluor^{TM} (10.4 g, 30 mmol) and anhydrous acetonitrile (100 cm^3) gave, after 16 h of heating, a yellow crude product mixture (6.4 g) which contained dimethyl pimelate (**78**) (90 area %), two isomers of dimethyl fluoropimelate (7 area %) in the ratio of 12 : 1; data as above and unidentified products (3 area %).

8.4 Fluorination of alkyl halide substrates using Selectfluor^{TM}

Attempted fluorination of 1-iodohexane (80). 1-Iodohexane (**80**) (5.0 g, 24 mmol), Selectfluor^{TM} (9.2 g, 26 mmol) and anhydrous acetonitrile (90 cm^3) gave, after 16 h of stirring, a red-purple reaction mixture which was decolourised using aqueous sodium metabisulite and then worked up as above to give a yellow crude product mixture (7.3 g) which contained > 30 unidentified products.

1-Bromo-3-, 4- and 5-fluorohexane (82A-C). 1-Bromohexane (**81**) (5.0 g, 30 mmol), Selectfluor^{TM} (11.8 g, 33 mmol), and anhydrous acetonitrile (120 cm^3) gave, after 16 h of heating, a yellow product mixture (7.9 g) which contained 1-bromo-3-, 4- and 5-fluorohexane (**82A-C**) (1.2 g, 75%, 30% conv.) in the ratio of 1.0 : 1.9 : 3.8 respectively, a trace amount of 1-bromo-6-fluorohexane; δ_F(188 MHz) -217.96 (m) and unidentified products. Purification of the crude product by preparative scale GC gave an analytically pure sample of 1-bromo-4-fluorohexane (**82B**) and 1-bromo-5-fluorohexane (**82C**) as an isomeric mixture and as a colourless liquid (Found C, 39.6; H, 6.7. $C_6H_{12}BrF$ requires: C, 39.4; H, 6.6%); NMR spectrum 24; Mass spectrum 23; IR spectrum 23.

1-Chloro-3-, 4- and 5-fluorohexane (84A-C). 1-Chlorohexane (**83**) (8.0 g, 67 mmol), Selectfluor^{TM} (26.0 g, 73 mmol), and anhydrous acetonitrile (260 cm^3) gave, after 19.5 h of heating, a yellow product mixture (8.2 g) which contained 1-chloro-3-, 4- and 5-fluorohexane (**84A-C**) (2.4 g, 56%, 53% conv.) in the ratio of 1.0 : 1.9 : 3.7 respectively, a trace amount of 1-chloro-6-fluorohexane; δ_F(188 MHz) -217.17 (m) and (> 5) unidentified products. Purification of the crude product by preparative scale GC gave an analytically pure sample of 1-chloro-5-fluorohexane (**84C**) and 1-chloro-4-fluorohexane (**84B**) as an isomeric mixture and as a colourless liquid (Found: C, 51.8; H, 8.7. $C_6H_{12}ClF$ requires: C, 52.0; H, 8.7%); NMR spectrum 23; Mass spectrum 22; IR spectrum 22.

8.5 Preparation and fluorination of decyltrimethylsilane (85)

Decyltrimethylsilane (85). Under an atmosphere of dry nitrogen, trimethylsilylchloride (6.5 g, 60 mmol) was added to a stirred solution which contained decylmagnesium bromide (12.3 g, 50 mmol) and anhydrous THF (70 cm^3). After addition of all the reagent, the resulting mixture was heated (70°C) for 30 min., then poured into saturated aqueous ammonium chloride and extracted with DCM (3 x 30 cm^3). The combined, dried ($MgSO_4$) organic extracts were reduced to give a pale yellow liquid (10.6 g). Purification of the mixture by distillation gave decyltrimethylsilane **(85)** (7.7 g, 72%) as a colourless liquid; bp 140-142°C/60mmHg (lit.,[157] 117°C/ 15 mmHg) (Found: C, 72.9; H, 14.1. $C_{13}H_{30}Si$ requires: C, 72.8; H, 14.1%); NMR spectrum 25; Mass spectrum 24; IR spectrum 24.

Fluorination of decyltrimethylsilane (85). Decyltrimethylsilane **(85)** (2.0 g, 10 mmol), elemental fluorine (30 mmol) and anhydrous acetonitrile (120 cm^3) gave, after the usual work-up, a yellow crude product mixture (3.3 g) which contained decyltrimethylsilane **(85)** (41 area %) and >15 unidentified products.

8.6 Oxidation of 1-aminohexane (86)

Using elemental fluorine. 1-aminohexane **(86)** (6.6 g, 65 mmol), elemental fluorine (39 mmol), and anhydrous acetonitrile (120 cm^3) gave, after the usual work-up, a brown crude product mixture (7.0 g) which contained hexanenitrile **(87)** (48 area %) and products which could not be identified (52 area %). Purifcation of the mixture by column chromatography using silica gel and DCM as the eluent gave hexanenitrile **(87)** (2.8 g, 44%, 100% conv.) as a colourless liquid; bp 162-164°C (lit.,[158] 162°C); R_f 0.80; (Found: C, 73.8; H, 11.4; N, 14.4. $C_6H_{11}N$ requires: C, 74.1; H, 11.4; N, 14.4%); NMR spectrum 26; Mass spectrum 25; IR spectrum 25.

Using Selectfluor™. Under an atmosphere of dry nitrogen, Selectfluor™ (11.6 g, 33 mmol) in acetonitrile (90 cm^3) was added dropwise to a stirred, cooled (-10°C) mixture which contained 1-aminohexane **(86)** (3.0 g, 30 mmol) and acetonitrile (30 cm^3). After addition of all the reagents the resultant mixture was allowed to self-heat and then work-up as usual to give a yellow crude product mixture (3.5 g) which contained > 30 unidentified product all in small amounts.

Repetition of this procedure at room temperature, 0°C and -40°C gave a very similar result.

Chapter 9: Experimental to Chapter 5

9.1 Preparation of quinoxaline derivatives

General Procedure. A solution of substituted phenylenediamine in water (55 cm^3), was added to a stirred, heated (70°C) solution of glyoxal sodium bisulfite addition compound monohydrate (glyoxal) in water (35 cm^3). After 1 h of heating (70°C) the reaction mixture was cooled to room temperature, neutralised with sodium carbonate and extracted with dichloromethane (3 x 30 cm^3). Solvent was evaporated from the combined, dried ($MgSO_4$) organic extracts to leave a crude product which was purified by distillation, recrystallisation or sublimation to give the quinoxaline. All yields quoted are for pure isolated products.

6-Methylquinoxaline (88). 4-Methyl-1,2-phenylenediamine (5.1 g, 42 mmol) and glyoxal (11.2 g, 42 mmol) gave an orange oil which was distilled to afford 6-methylquinoxaline **(88)** (4.4 g, 73%) as a pale yellow oil; bp 125°C/14 mmHg (lit.,[159] 141.5/29 mmHg) (Found: M^+, 144.0687. $C_9H_8N_2$ requires: M^+, 144.0687); NMR spectrum no. 27 ($^{13}C^{140}$); Mass spectrum no. 26; IR spectrum no. 26.

6,7-Dimethylquinoxaline (89). 4,5-Dimethyl-1,2-phenylenediamine (2.9 g, 21 mmol) and glyoxal (5.6 g, 21 mmol) gave after recrystallisation 6,7-dimethylquinoxaline **(89)** (2.6 g, 78%) as a white solid; mp 96-98°C (from ethanol) (lit.,[160] 95-98°C) (Found: C, 75.9; H, 6.2; N, 17.4. $C_{10}H_{10}N_2$ requires: C, 75.9; H, 6.4; N, 17.7%); NMR spectrum no. 28 ($^{13}C^{161}$); Mass spectrum no. 27; IR spectrum no. 27.

6-Chloroquinoxaline (90). 4-Chloro-1,2-phenylenediamine (5.0 g, 35 mmol) and glyoxal (10.0 g, 35 mmol) gave after sublimation (vacuum sublimation oil bath temp. 45°C/<1 mmHg) 6-chloroquinoxaline **(90)** (4.6 g, 79%) as a white solid; mp 62-63°C (lit.,[159] 63.8-64.3°C) (Found: C, 58.3; H, 3.1; N, 17.0. $C_8H_5ClN_2$ requires: C, 58.3; H, 2.9; N, 17.0%); NMR spectrum no. 29[140]; Mass spectrum no. 28; IR spectrum no. 28.

6,7-Dichloroquinoxaline (91). 4,5-Dichloro-1,2-phenylenediamine (3.7 g, 21 mmol) and glyoxal (5.6 g, 21 mmol) gave after recrystallisation 6,7-dichloroquinoxaline **(91)** (3.3 g, 78%) as white lustrous needles; mp 209-210°C (from acetone) (lit.,[162] 210°C) (Found: C, 48.0; H, 1.9; N, 13.8. $C_8H_4Cl_2N_2$ requires: C, 48.2; H, 2.1; N, 14.1%); NMR spectrum no. 30; Mass spectrum no. 29; IR spectrum no. 29.

6-Methoxyquinoxaline (92). 4-Methoxy-1,2-phenylenediamine (2.6 g, 24 mmol) and glyoxal (6.8 g, 24 mmol) gave after vacuum sublimation (vacuum sublimation oil bath temp. 80°C/<1 mmHg) 6-methoxyquinoxaline **(92)** (3.2 g, 82%) as white needles; mp 61-62°C (lit.,[159] 61-62°C) (Found: C, 67.1; H, 5.0; N, 17.4.

$C_9H_8N_2O$ requires: C, 67.4; H, 5.0; N, 17.5%); NMR spectrum no. 31 ($^{13}C^{140}$); Mass spectrum no. 30; IR spectrum no. 30.

6-Nitroquinoxaline (93). 4-Nitro-1,2-phenylenediamine (3.2 g, 21 mmol) and glyoxal (5.6 g, 21 mmol) gave after recrystallisation 6-nitroquinoxaline **(93)** (3.3 g, 89%) as white needles; mp 177-178°C (from ethanol) (lit.,[163] 177-179°C) (Found: C, 54.6; H, 2.9; N, 24.1. $C_8H_5N_3O_2$ requires: C, 54.8; H, 2.9; N, 24.0%); NMR spectrum no. 32 ($^{13}C^{140}$); Mass spectrum no. 31; IR spectrum no. 31.

9.2 Fluorination of quinoxaline derivatives

General procedure. A mixture containing quinoxaline, iodine, and triethylamine in Freon 113 (1,1,2-trichlorotrifluoroethane) (160 cm^3) was placed in the fluorination apparatus and elemental fluorine, as a 10% (v/v) mixture in nitrogen, was passed through the stirred, cooled (0°C) mixture using PTFE tubing at *ca.* 30 cm^3min^{-1}. Preceding and following fluorination, the reaction mixture was purged with nitrogen. After the final nitrogen purge, trichlorotrifluoroethane was removed by distillation from the reaction mixture, and dichloromethane (100 cm^3) was added. The resulting mixture was poured into 10% aqueous sodium metabisulfite, neutralised with sodium hydrogen carbonate and extracted continuously with dichloromethane. The organic extract was dried ($MgSO_4$) and evaporated to leave a brown crude product. The crude product was analysed by GC-MS and by ^{19}F NMR with reference to a fluorobenzene internal standard (as detailed in Chapter 6) to give the yield and conversion values. Pure fluoroquinoxaline was isolated by column chromatography on silica gel using dichloromethane (for fluoroquinoxaline derivatives) or 1:1 dichloromethane-hexane (for difluoroquinoxaline derivatives) as the eluent.

2-Fluoroquinoxaline (95). Quinoxaline **(94)** (3.9 g, 30 mmol), iodine (7.6 g, 30 mmol), triethylamine (3.0 g, 30 mmol), and fluorine (45 mmol) gave 2-fluoroquinoxaline **(95)** (1.9 g, 48%, 91% conv.) as a pale yellow oil; R_f 0.60; bp 120°C/8 mmHg (lit.,[164] 180-182°C/25 mmHg) (Found: M^+, 148.0437. $C_8H_5FN_2$ requires M, 148.0437); NMR spectrum no. 33; Mass spectrum no. 32; IR spectrum no. 32 and, after sublimation (vacuum sublimation oil bath temp. 60°C/<1 mmHg), 2,3-difluoroquinoxaline **(100)** (0.5 g, 11%) as a white solid; mp 89-90°C (lit.,[136] 94-95°C); R_f 0.82 (Found: C, 57.5; H, 2.3; N, 16.8. $C_8H_4F_2N_2$ requires: C, 57.8; H, 2.4; N, 16.9%); NMR spctrum no. 39; Mass spectrum no. 36; IR spectrum no. 36.

2-Fluoro-6-methylquinoxaline (96A) and 2-fluoro-7-methylquinoxaline (96B). 6-Methylquinoxaline **(88)** (4.1 g, 29 mmol), iodine (7.3 g, 29 mmol), triethylamine (2.9 g, 29 mmol), and fluorine (35 mmol) gave after sublimation (vacuum sublimation oil bath temp. 30°C/<1 mmHg) an isomeric mixture of 2-fluoro-6-methylquinoxaline **(96A)** (0.3 g, 16%) and 2-fluoro-7-methylquinoxaline **(96B)** (0.6

g, 29%, 43% conv.) as white needles; mp 61-63°C; R_f 0.58 (Found: M^+, 162.0593. $C_9H_7FN_2$ requires: M^+, 162.0593); 2-fluoro-6-methylquinoxaline (**96A**) NMR spectrum no. 34; 2-fluoro-7-methylquinoxaline (**96B**) NMR spectrum no. 35; 2-fluoro-6-methylquinoxaline (**96A**) and 2-fluoro-7-methylquinoxaline (**96B**); Mass spectrum no. 33; IR spectrum no. 33 and, 2,3-difluoro-6-methylquinoxaline (**101**) (0.2 g, 7%) as a white solid; mp 81-82°C; R_f 0.64 (Found: C, 59.8; H, 3.3; N, 15.4. $C_9H_6F_2N_2$ requires: C, 60.0; H, 3.4; N, 15.6%); NMR spectrum no. 40; Mass spectrum no. 37; IR spectrum no. 37.

2-Fluoro-6,7-dimethylquinoxaline (97). 6,7-Dimethyquinoxaline (**89**) (1.6 g, 10 mmol), iodine (2.6 g, 10 mmol), triethylamine (1.0 g, 10 mmol) and fluorine (15 mmol) gave after sublimation (vacuum sublimation oil bath temp. 60°C/<1 mmHg) 2-fluoro-6,7-dimethylquinoxaline (**97**) (0.3 g, 40%, 75% conv.) as a white solid; mp 94-95°C; R_f 0.54 (Found: C, 68.1; H, 5.0; N, 16.0. $C_{10}H_9FN_2$ requires: C, 68.2; H, 5.2; N, 15.9%); NMR spectrum no. 36; Mass spectrum no. 34; IR spectrum 34 and, after sublimation (vacuum sublimation oil bath temp. 50°C/<1 mmHg) 2,3-difluoro-6,7-dimethylquinoxaline (**102**) (0.1 g, 5%) as a white solid; mp 150-151°C; R_f 0.61 (Found: C, 61.4; H, 4.0; N, 14.4. $C_{10}H_8F_2N_2$ requires: C, 61.6; H, 4.2; N, 14.4%); NMR spectrum no. 41; Mass spectrum no. 38; IR spectrum no. 38.

6-Chloro-2-fluoroquinoxaline (98A) and 7-chloro-2-fluoroquinoxaline (98B). 6-Chloroquinoxaline (**90**) (1.8 g, 11 mmol), iodine (2.7 g, 11 mmol), triethylamine (1.1 g, 11 mmol), and fluorine (15 mmol) gave after sublimation (vacuum sublimation oil bath temp. 50°C/<1 mmHg) an isomeric mixture of 6-chloro-2-fluoroquinoxaline (**98A**) (0.4 g, 28 %) and 7-chloro-2-fluoroquinoxaline (**98B**) (0.2 g, 16%, 64% conv.) as white needles; mp 98-100°C; R_f 0.53 (Found: C, 52.4; H, 2.1; N, 15.1. $C_8H_4ClFN_2$ requires: C, 52.7; H, 2.2; N, 15.4%); 6-chloro-2-fluoroquinoxaline (**98A**) NMR spectrum no. 37; 7-chloro-2-fluoroquinoxaline (**98B**) NMR spetrum no. 38; 6-chloro-2-fluoroquinoxaline (**98A**) and 7-chloro-2-fluoroquinoxaline (**98B**) Mass spectrum no. 35; IR spectrum no. 35 and, 6-chloro-2,3-difluoroquinoxaline (**103**) (0.04 g, 3%) as a white solid; mp 89-90°C; R_f 0.60 (Found: C, 48.1; H, 1.5; N, 13.9. $C_8H_3ClF_2N_2$ requires: C, 47.9; H, 1.5; N, 14.0%); NMR spectrum no. 42; Mass spectrum no. 39; IR spectrum no. 39.

2-Fluoro-6-methoxyquinoxaline (99A) and 2-fluoro-7-methoxoquinoxaline (99B). 6-Methoxyquinoxaline (**92**) (1.3 g, 8 mmol), iodine (2.1 g, 8 mmol), triethylamine (0.8 g, 8 mmol), and fluorine (12 mmol) gave after purification, a product mixture which contained an isomeric mixture of 2-fluoro-6-methoxyquinoxaline (**99A**) and 2-fluoro-7-methoxyquinoxaline (**99B**) (0.3 g, 43%, 55% conv.) in the ratio of 1.0 : 7.5 not necasasarily respectively; R_f 0.53 (Found: M^+, 178.0542. $C_9H_7FN_2$ requires: M^+, 178.0542); δ_F(376 MHz) -74.80 (d, $^3J_{HF}$ 7.6),

-77.30 (d, $^3J_{HF}$ 7.6); *m/z* (EI^+) 178 (M^+, 100%), 135 (78), and difluoromethoxyquinoxaline (11% by GC) (Found: M^+, 196.0448. $C_9H_6F_2N_2$ requires: M^+, 196.0448); δ_F(188 MHz) -151.84 (t, $^2J_{HF}$ 57.1, CH_2F), -152.20 (t, $^2J_{HF}$ 56.1, CH_2F); *m/z* (EI^+) 196 (M^+, 100%), 153 (100).

2,3-Difluoroquinoxaline (100). Quinoxaline **(94)** (3.3 g, 25 mmol), iodine (6.4 g, 25 mmol), triethylamine (5.1 g, 50 mmol), and fluorine (75 mmol) gave 2,3-difluoroquinoxaline **(100)** (1.1 g, 33%, 100% conv.); data as above and 2-fluoroquinoxaline **(95)** (0.6 g, 16%); data as above.

2,3-Difluoro-6-methylquinoxaline (101). 6-Methyquinoxaline **(88)** (1.6 g, 11 mmol), iodine (2.7 g, 11 mmol), triethylamine (2.2 g, 22 mmol), and fluorine (33 mmol) gave 2,3-difluoro-6-methylquinoxaline **(101)** (0.3 g, 23%, 71% conv.); data as above; and, fluoromethylquinoxaline **(96A, B)** (0.3 g, 16%); data as above.

2,3-Difluoro-6,7-dimethylquinoxaline (102). 6,7-Dimethylquinoxaline **(89)** (1.8 g, 11 mmol), iodine (2.9 g, 11 mmol), triethylamine (2.3 g, 22 mmol), and fluorine (33 mmol) gave 2,3-difluoro-6,7-dimethylquinoxaline **(102)** (0.2 g, 12%, 90% conv.); data as above and, 2-fluoro-6,7-dimethylquinoxaline **(97)** (0.2 g, 14%); data as above.

6-Chloro-2,3-difluoroquinoxaline (103). 6-Chloroquinoxaline **(90)** (2.2 g, 14 mmol), iodine (3.4 g, 14 mmol), triethylamine (2.7 g, 28 mmol), and fluorine (42 mmol) gave 6-chloro-2,3-difluoroquinoxaline **(103)** (0.5 g, 19%, 94% conv.); data as above and, chlorofluoroquinoxaline **(98A, B)** (0.6 g, 25%); data as above.

9.3 Attempted fluorination of quinoxaline derivatives

6-Nitroquinoxaline (93). 6-Nitroquinoxaline **(93)** (0.7 g, 4 mmol), iodine (1.0 g, 4 mmol), triethylamine (0.4 g, 4 mmol), and fluorine (6 mmol) gave 6-nitroquinoxaline **(93)** only.

6,7-Dichloroquinoxaline (91). 6,7-Dichloroquinoxaline **(91)** (1.5 g, 8 mmol), iodine (1.9 g, 8 mmol), triethylamine (0.8 g, 8 mmol), and fluorine (12 mmol) gave 6,7-dichloroquinoxaline **(91)** only.

9.4 Attempted fluorination of diazines

General procedure. As for fluorination of quinoxaline until purification of the crude product mixture using, diazine (3.0 g, 37 mmol), iodine (9.4 g, 37 mmol), and triethylamine (3.7 g, 37 mmol) in 1,1,2-trichlorotrifluoroethane (160 cm^3) and elemental fluorine (75 mmol).

Pyridazine (104). Crude product mixture contained a trace of fluoropyridazine; *m/z* (EI^+) 98 (M^+, 100%), 86 (20) and pyridazine **(104)**.

Pyrimidine (105). Crude product contained pyrimidine **(105)** only.

Pyrazine (106). Crude product contained fluoropyrazine (0.1 g, <3%); δ_F(235MHz) -79.8 (s); m/z (EI^+) 98 (M^+, 100%) (which co-elutes with triethylamine) and pyrazine **(106)**.

9.5 Solvent survey

General procedure. As for fluorination of quinoxaline until purification of the crude product mixture.

α,α,α-Trifluoromethylbenzene. Quinoxaline **(94)** (3.9 g, 30 mmol), iodine (7.6 g, 30 mmol), triethylamine (3.0 g, 30 mmol), and fluorine (45 mmol) in trifluorotoluene (160 cm^3) gave a crude product mixture which contained 2-fluoroquinoxaline **(95)** (0.2 g, 6%, 65% conv.); data as above and, 2,3-difluoroquioxaline **(100)** (0.02 g, <1%); data as above.

Hexafluorobenzene. Quinoxaline **(94)** (1.3 g, 10 mmol), iodine (2.5 g, 10 mmol), triethylamine (1.0 g, 10 mmol), and fluorine (15 mmol) in hexafluorobenzene (160 cm^3) gave a crude product mixture which contained 2-fluoroquinoxaline **(95)** (0.6 g, 26%, 49% conv.); data as above and 2,3-difluoroquioxaline **(100)** (0.1 g, 2%); data as above.

Dichloromethane. 4-Ethylpyridine **(107)** (1.6 g, 15 mmol), iodine (3.8 g, 15 mmol), triethylamine (1.5 g, 15 mmol), and fluorine (20 mmol) in dichloromethane (160 cm^3) gave a crude product mixture which contained no ethylfluoropyridine (by GC-MS and ^{19}F NMR).

Tetrahydrofuran, N,N-dimethylformamide and nitromethane. Quinoxaline **(94)** (1.0 g, 8 mmol), iodine (1.9 g, 8 mmol), triethylamine (0.8 g, 8 mmol), and fluorine (15 mmol) in tetrahydrofuran, N,N-dimethylformamide or nitromethane (40 cm^3) gave quinoxaline only.

Appendices

Appendix 1: NMR Spectra

No. 36 2-Fluoro-6,7-dimethylquinoxaline (**97**)

No. 37 6-Chloro-2-fluoroquinoxaline (**98A**)

No. 38 7-Chloro-2-fluoroquinoxaline (**98B**)

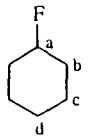
No. 39 2,3-Difluoroquinoxaline (**100**)

No. 40 2,3-Difluoro-6-methylquinoxaline (**101**)

No. 41 2,3-Difluoro-6,7-dimethylquinoxaline (**102**)

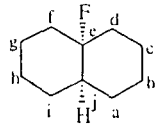
No. 42 2,3-Difluoro-6-chloroquinoxaline (**103**)

No. 1 Fluorocyclohexane (37)



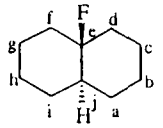
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-171.47	br s	-	-	-
^{1}H				
1.30 - 1.75	m	-	10	b, c and d
4.57	dm	$^{2}J_{HF}$ 48.8 $^{3}J_{HF}$ and $^{4}J_{HF}$ 3.6	1	a
^{13}C				
22.8	d	$^{3}J_{CF}$ 7.7	-	c
25.2	d	$^{4}J_{CF}$ 1.5	-	d
32.3	d	$^{2}J_{CF}$ 18.7	-	b
91.5	d	$^{1}J_{CF}$ 169.8	-	a

No. 2 *cis*-9-Fluorodecalin (47)



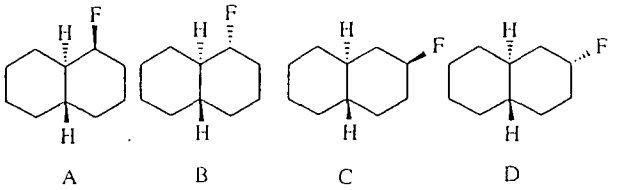
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-140.57	m	-	-	-
^{1}H				
1.20 - 1.85	m	-	-	-
^{13}C				
20.0-38.1	br s	-	-	remaining C
40.8	d	$^{2}J_{CF}$ 19.5	-	d, f, or j
96.9	d	$^{1}J_{CF}$ 169.8	-	e

No. 3 *trans*-9-Fluorodecalin (49)



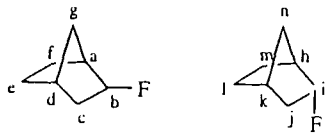
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-177.11	m	-	-	-
^{1}H				
1.15 - 1.80	m		-	-
^{13}C				
21.6	d	$^{3}J_{CF}$ 1.5	-	c and g
25.8	s	-	-	b and h
28.7	d	$^{3}J_{CF}$ 1.1	-	a and i
37.1	d	$^{2}J_{CF}$ 23.4	-	d and f
43.1	d	$^{2}J_{CF}$ 21.5	-	j
94.5	d	$^{1}J_{CF}$ 172.7	-	e

No. 4 *trans*-1- and 2-Fluorodecalin (63A-D)



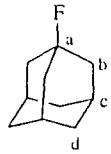
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-167.97	dd	$^{2}J_{HF}$ 49.5 $^{3}J_{HF}$ 4.5	1.36	C
-177.34	d	$^{2}J_{HF}$ 49.3	1.14	B
-183.07	tq	$^{2}J_{HF}$ and $^{3}J_{HF}$ 46.7 $^{3}J_{HF}$ 8.7	2.24	D
-196.60	mq	$^{2}J_{HF}$ 49.6	1.00	A
^{1}H				
0.60 - 2.10	m	-	113.97	CH and CH_2
4.08	dddd	$^{2}J_{HF}$ 49.8 $^{3}J_{HH}$ 10.8 $^{3}J_{HH}$ 9.9 $^{3}J_{HH}$ 4.8	1.16	CHF-B
4.47	dtt	$^{2}J_{HF}$ 49.2 $^{3}J_{HH}$ 10.8 $^{3}J_{HH}$ 4.8	1.47	CHF-C
4.54	ddt	$^{2}J_{HF}$ 49.2 $^{3}J_{HH}$ 3.2 $^{3}J_{HF}$ 2.0	1.00	CHF-A
4.87	d sept	$^{2}J_{HF}$ 48.4 $^{3}J_{HH}$ 2.0	2.40	CHF-D

No. 6 *exo*- and *endo*-2-Fluoronorbornane (43A, B)



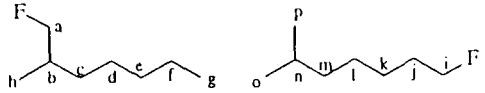
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-160.48	m	-	-	b
-189.85	m	$^{2}J_{HF}$ 57.9		i
		$^{3}J_{HF}$ 29.3		
		$^{3}J_{HF}$ 16.2		
^{1}H				
0.91 - 2.49	m	-	20	CH and CH_2
4.58	dm	$^{2}J_{HF}$ 56.4	1	b
5.02	dm	$^{2}J_{HF}$ 57.9	1	i
^{13}C				
19.9	d	$^{3}J_{CF}$ 10.3		m
22.3	d	$^{3}J_{CF}$ 10.3		f
27.9	s	-	-	e
29.1	s	-	-	l
34.7	d	$^{3}J_{CF}$ 1.2	-	g
34.8	s	-	-	d
36.5	d	$^{3}J_{CF}$ 2.3	-	k
36.9	d	$^{3}J_{CF}$ 4.9	-	n
37.2	d	$^{2}J_{CF}$ 22.1	-	j
39.9	d	$^{2}J_{CF}$ 19.8	-	c
41.2	d	$^{2}J_{CF}$ 17.5	-	h
42.0	d	$^{2}J_{CF}$ 19.4	-	a
94.7	d	$^{1}J_{CF}$ 184.0	-	i
96.2	d	$^{1}J_{CF}$ 181.6	-	b

No. 7 1-Fluoroadamantane (44)



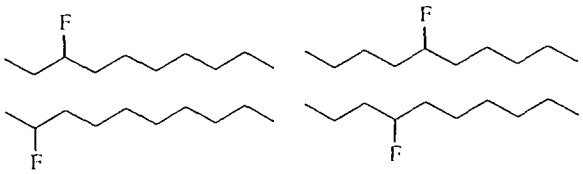
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-128.80	s	-	-	-
^{1}H				
1.62	m	-	2	d
1.88	m	-	2	b
2.23	s	-	1	c
^{13}C				
31.7	d	$^{3}J_{CF}$ 9.9	-	c
36.1	d	$^{4}J_{CF}$ 1.9	-	d
43.0	d	$^{2}J_{CF}$ 17.2	-	b
92.8	d	$^{1}J_{CF}$ 183.1	-	a

1-Fluoro-6-methylheptane (51B)



Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
218.38	m	24.8	1.0	i
222.65	dt	$^{2}J_{HF}$ 47.8, $^{3}J_{HF}$ 18.8	1.7	a
^{1}H				
0.80-1.00	m	-	16.7	CH_3 and/ or CH_2
1.05-1.85	m	-	26.5	CH_3 and/or CH_2 and/or CH
4.26	dm	$^{2}J_{HF}$ 48.0	1.7	a
4.44	dm	$^{2}J_{HF}$ 47.6	2	i
^{13}C				
14.1	s	-	-	CH_3
15.8	s	-	-	CH_3
15.9	s	-	-	CH_3
22.6	s	-	-	CH_2
25.4	d	$^{3}J_{CF}$ 5.4	-	c or k
26.5	s	-	-	CH_2
27.0	s	-	-	CH_2
27.9	s	-	-	n
30.4	d	$^{2}J_{CF}$ 19.5	-	j
32.0	s	-	-	CH_2
32.3	d	$^{3}J_{CF}$ 5.8	-	c or k
34.0	d	$^{2}J_{CF}$ 18.1	-	b
38.8	s	-	-	CH_2
84.3	d	$^{1}J_{CF}$ 164.7	-	a
88.3	d	$^{1}J_{CF}$ 168.9	-	i

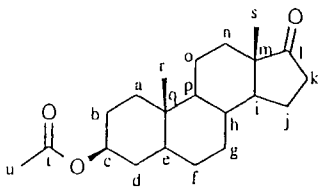
No. 9 2-, 3-, 4-, and 5-Fluorodecane (53A-D)



Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-172.46	m	19.2	2.39	-
-180.38	m	17.3	1.27	-
-180.71	m	17.2	1.00	-
-181.62	m	18.8	1.09	-
^{1}H				
0.85 - 0.98	m	-	4.49	CH_2 and CH_3
1.24 - 1.70	m	-	14.84	CH_2 and CH_3
4.30 - 4.74	m	-	1.00	CHF

^{13}C				
9.4	s	-	-	CH_3
9.4	s	-	-	CH_3
13.9	s	-	-	CH_3
14.0	s	-	-	CH_3
14.1	s	-	-	CH_3
18.4	d	4.6	-	CH_2
21.0	d	22.9	-	CHFCH_3
22.6	s	-	-	CH_2
22.7	s	-	-	CH_2
24.8	d	4.6	-	CH_2
25.2	s	-	-	CH_2
25.6	d	5.0	-	CH_2
27.3	d	4.6	-	CH_2
28.1	d	21.3	-	CHFCH_2
29.2	d	2.6	-	CH_2
29.2	s	-	-	CH_2
29.5	d	1.2	-	CH_2
29.7	s	-	-	CH_2
31.7	d	4.2	-	CH_2
31.8	d	4.1	-	CH_2
31.9	s	-	-	CH_2
34.7	d	20.5	-	CHFCH_2
34.9	d	20.9	-	CHFCH_2
35.1	d	21.0	-	CHFCH_2
35.2	d	20.5	-	CHFCH_2
36.9	d	20.6	-	CHFCH_2
37.3	d	21.0	-	CHFCH_2
91.1	d	164.1	-	CHF
94.4	d	166.4	-	CHF
94.6	d	166.4	-	CHF
95.8	d	166.1	-	CHF

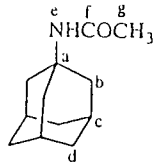
No. 10 3-β-Acetoxy-5α-androstanone (55)



Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^1H				
0.71	m	-	1	p
0.84	s	-	3	r
0.85	s	-	3	s
1.00	m	-	2	one of a and one of n
1.63	m	-	2	one of d and one of o
1.92	m	-	1	one of j
2.02	s	-	3	u
2.06	m	-	1	one of k
2.43	m	-	1	one of k
4.70	m	-	1	c
2.10 - 2.43	mm	-	14	remaining H

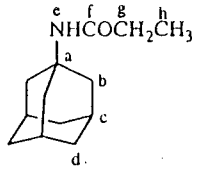
^{13}C				
12.2	s	-	-	r
13.8	s	-	-	s
20.4	s	-	-	o
21.5	s	-	-	u
21.8	s	-	-	j
27.4	s	-	-	b
28.4	s	-	-	f
30.8	s	-	-	n
31.5	s	-	-	g
33.9	s	-	-	d
35.0	s	-	-	h
35.6	s	-	-	q
35.8	s	-	-	k
36.7	s	-	-	a
44.6	s	-	-	e
47.7	s	-	-	m
51.3	s	-	-	i
54.3	s	-	-	p
73.5	s	-	-	c
170.7	s	-	-	t
221.30	s	-	-	l

No. 11 N-(1-Adamantyl)acetamide (65)



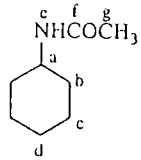
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{1}H				
1.66	s	-	6	d
1.89	s	-	3	g
1.97	s	-	6	b
2.05	m	-	3	c
5.20	br s	-	1	e
^{13}C				
24.7	s	-	-	g
29.4	s	-	-	c
36.3	s	-	-	d
41.6	s	-	-	b
51.8	s	-	-	a
169.3	s	-	-	f

No. 12 N-(1-Adamantyl)propylamide (66)



Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{1}H				
1.04	t	$^3J_{HH}$ 8.0	3	g
1.61	br s	-	6	b or d
1.94	br s	-	6	b or d
2.00	br s	-	3	c
2.07	q	$^3J_{HH}$ 8.0	2	g
5.23	br s	-	1	e
^{13}C				
9.8	s	-	-	h
29.3	s	-	-	c
30.4	s	-	-	g
36.2	s	-	-	d
41.5	s	-	-	b
51.4	s	-	-	a
173.9	s	-	-	f

No. 13 N-(Cyclohexyl)acetamide (67)

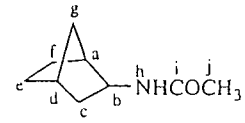


Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{1}H				
1.06-1.20	m	-	3	remaining H
1.28-1.40	m	-	2	"
1.55-1.73	m	-	3	"
1.85-1.90	m	-	2	"
1.94	s	-	3	g
3.74	m	-	1	a
5.43	br s	-	1	e
^{13}C				
23.6	s	-	-	g
24.8	s	-	-	b, c, or d
25.5	s	-	-	b, c or d
33.2	s	-	-	b, c or d
48.2	s	-	-	a
169.0	s	-	-	f

No. 14 N-(*trans*-9-Decalyl)acetamide (68)

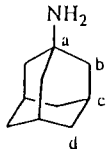
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{1}H				
0.80 - 1.62	m	-	-	
2.57	s	-	1	
2.62	s	-	1	
4.90	br s	-	1	g
^{13}C				
21.6	s	-	-	b, c, d or e
24.6	s	-	-	i
26.1	s	-	-	b, c, d or e
28.6	s	-	-	b, c, d or e
34.4	s	-	-	b, c, d or e
45.2	s	-	-	f
55.9	s	-	-	a
169.3	s	-	-	h

No. 15 N-(*exo*-2-Norbornyl)acetamide (69)



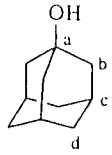
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{1}H				
1.80	m	-	1	c
1.94	s	-	3	j
2.19	m	-	1	a
2.27	m	-	1	d
3.71	dt	$^3J_{HH}$ 7.6 $^3J_{HH}$ and $^4J_{HH}$ 3.6	1	b
5.35	br s	-	1	h
1.08 - 1.55	m	-	7	remaining H
^{13}C				
23.8	s	-	-	j
26.4	s	-	-	f
27.1	s	-	-	e
35.6	s	-	-	g
35.7	s	-	-	d
40.5	s	-	-	c
42.3	s	-	-	a
52.8	s	-	-	b
169.4	s	-	-	i

No. 16 1-Aminoadamantane (70)



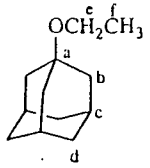
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^1H				
1.50	br s	-	2	NH_2
1.55	m	-	2	b
1.57	m	-	2	d
2.02	m	-	1	c
^{13}C				
29.7	s	-	-	c
36.2	s	-	-	d
46.2	s	-	-	b
47.2	s	-	-	a

No. 17 1-Hydroxyadamantane (71)



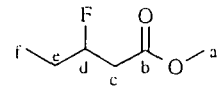
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^1H				
1.42	br s	-	1	OH
1.62	m	-	2	d
1.72	m	-	2	b
2.14	br s	-	1	c
^{13}C				
31.0	s	-	-	c
36.3	s	-	-	d
45.6	s	-	-	b
68.5	s	-	-	a

No. 18 1-Ethoxyadamantane (72)



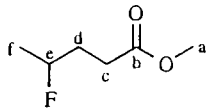
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{1}H				
1.10	t	$^{3}J_{HH}$ 7.2	3	f
1.55	m	-	2	d
1.68	d	J_{HH} 2.8	2	b
2.07	br s	-	1	c
3.40	q	$^{3}J_{HH}$ 7.2	2	e
^{13}C				
16.4	s	-	-	f
30.5	s	-	-	c
36.5	s	-	-	d
41.6	s	-	-	b
54.9	s	-	-	e
71.9	s	-	-	a

No. 19 Methyl 3-fluorovalerate (74A)



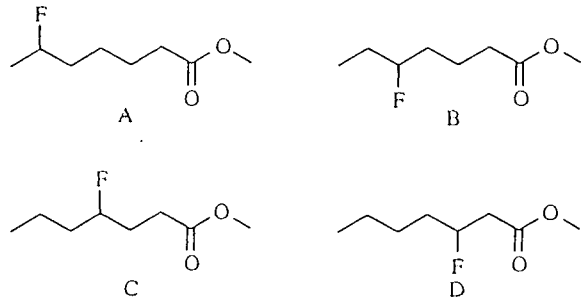
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-181.30	m	-	-	-
^{1}H				
0.98	t	$^{3}J_{HH}$ 7.2	3	f
1.65	m	-	2	e
2.63	m	-	2	c
3.65	s	-	3	a
4.81	dm	$^{2}J_{HF}$ 48.4	1	d
^{13}C				
9.0	s	-	-	f
27.8	d	$^{2}J_{CF}$ 21.0	-	e
39.8	d	$^{2}J_{CF}$ 24.1	-	c
51.8	s	-	-	a
91.4	d	$^{1}J_{CF}$ 170.9	-	d
174.3	s	-	-	b

No. 20 Methyl 4-fluorovalerate (74B)



Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-176.07	m	-	-	-
^{1}H				
1.31	d	$^{3}J_{HH}$ 6.4	3	f
1.78-1.90	m	-	2	d
2.40	m	-	2	c
3.62	s	-	3	a
4.62	dm	$^{2}J_{HF}$ 49.2	1	e
^{13}C				
20.8	d	$^{2}J_{CF}$ 22.6	-	f
29.6	d	$^{4}J_{CF}$ 4.5	-	c
31.9	d	$^{2}J_{CF}$ 21.4	-	d
51.6	s	-	-	a
89.9	d	$^{1}J_{CF}$ 166.2	-	e
173.5	s	-	-	b

No. 21 Methyl 3-, 4-, 5-, and 6-fluoroenanthate (76A-D)

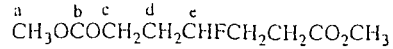


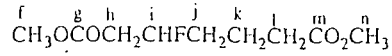
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-173.14	m	-	13.7	A
-180.08	m	-	1.0	C
-182.84	m	-	4.6	B
-183.62	m	-	2.1	D
^{1}H				
0.80-1.00	m	-	1.0	CH_2 and/or CH_3
1.27-1.65	m	-	7.0	CH_2 and/or CH_3
2.30-2.38	m	-	3.0	CH_2 and/or CH_3
3.67-6.68	m	-	3.0	OCH_3
4.25-5.02	m	-	1.0	CHF

^{13}C				
9.6	d	J_{CF} 4.9	-	CH_3-B, C or D
14.1	s	-	-	CH_3-B, C or D
14.2	s	-	-	CH_3-B, C or D
18.5	s	-	-	CH_2
18.6	s	-	-	CH_2
20.9	d	J_{CF} 4.1	-	CH_2
21.2	d	$^2J_{CF}$ 22.9	-	CH_3-A
24.9	d	J_{CF} 5.0	-	CH_2
27.2	d	J_{CF} 4.2	-	CH_2
28.5	d	$^2J_{CF}$ 21.4	-	*CH_2*CHF
29.9	d	J_{CF} 4.2	-	CH_2
30.5	d	$^2J_{CF}$ 21.4	-	*CH_2*CHF
33.9	s	-	-	CH_2
34.2	d	$^2J_{CF}$ 21.0	-	*CH_2*CHF
34.8	d	$^2J_{CF}$ 20.2	-	*CH_2*CHF
36.8	d	$^2J_{CF}$ 20.6	-	*CH_2*CHF-A
37.4	d	$^2J_{CF}$ 20.6	-	*CH_2*CHF
40.5	d	$^2J_{CF}$ 24.0	-	*CH_2*CHF
51.7	s	-	-	OCH_3
51.8	s	-	-	OCH_3
51.8	s	-	-	OCH_3
51.9	s	-	-	OCH_3
90.6	d	$^1J_{CF}$ 169.4	-	CHF-C
91.0	d	$^1J_{CF}$ 164.5	-	CHF-A
92.4	d	$^1J_{CF}$ 167.9	-	CHF-D
95.4	d	$^1J_{CF}$ 167.5	-	CHF-B
173.9	s	-	-	CO-D
174.1	s	-	-	CO-B
174.3	s	-	-	CO-A
174.6	s	-	-	CO-C

A15

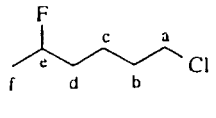
No. 22 Dimethyl 3-fluoropimelate (79A) and Dimethyl 4-fluoropimelate (79B)



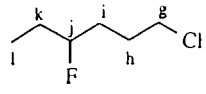


Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-187.99	m	-	1.0	i
-192.22	m	-	1.7	e
^1H				
1.60-1.99	m	-	10.5	CH_2
2.26-2.88	m	-	11.1	CH_2
3.66	s	-	3.0	f or n
3.67	s	-	10.2	a
3.70	s	-	3.0	f or n
4.53	dm	$^2J_{HF}$ 49.6	1.7	e
4.93	dm	$^2J_{HF}$ 48.0	1.0	i
^{13}C				
20.6	d	$^3J_{CF}$ 4.2	-	k
29.8	d	$^3J_{CF}$ 4.5	-	c
30.7	d	$^2J_{CF}$ 21.0	-	d
33.6	s	-	-	l
34.3	d	$^2J_{CF}$ 20.9	-	j
40.5	d	$^2J_{CF}$ 24.0	-	h
51.8	s	-	-	f or n
51.9	s	-	-	a
52.2	s	-	-	f or n
90.1	d	$^1J_{CF}$ 170.2	-	i
92.5	d	$^1J_{CF}$ 169.0	-	e
170.7	d	$^3J_{CF}$ 6.1	-	g
173.6	s	-	-	b

No. 23 1-Chloro-4-fluorohexane (84B) and 1-Chloro-5-fluorohexane (84C)



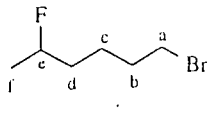
A



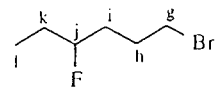
B

Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-173.29	m	-	3.7	e
-182.64	m	-	1.0	j
^{1}H				
0.90-1.00	m	-	5.3	CH_2 and/or CH_3
1.29-2.10	m	-	41.7	CH_2 and/or CH_3
3.55	m	-	4.7	CHCl
4.42	dm	$^{2}J_{HF}$ 49.5	1.0	j
4.68	dm	$^{2}J_{HF}$ 48.5	3.7	e
^{13}C				
21.0	d	$^{2}J_{CF}$ 20.9	-	f
22.5	d	$^{3}J_{CF}$ 5.0	-	c
32.3	s	-	-	b
36.1	d	$^{2}J_{CF}$ 21.0	-	d
44.8	s	-	-	a
90.7	d	$^{1}J_{CF}$ 164.4	-	e
9.33	d	$^{3}J_{CF}$ 6.4	-	l
28.1	d	$^{2}J_{CF}$ 21.0	-	i or k
28.3	d	$^{3}J_{CF}$ 3.8	-	h
32.0	d	$^{2}J_{CF}$ 21.3	-	i or k
44.9	s	-	-	g
94.9	d	$^{1}J_{CF}$ 168.3	-	j

No. 24 1-Bromo-4-fluorohexane (82B) and 1-Bromo-5-fluorohexane (82C)



A



B

Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-171.83	m	-	2.5	A
-181.18	m	-	1.0	B
^{1}H				
0.85-1.00	m	-	3.9	CH_2 and CH_3
1.29-2.05	m	-	31.1	CH_2 and CH_3
3.42	m	-	3.5	CHBr
4.43	dm	$^{2}J_{HF}$ 49.2	1.0	CHF-B
4.66	dm	$^{2}J_{HF}$ 48.8	2.5	CHF-A
^{13}C				
21.0	d	$^{2}J_{CF}$ 22.8	-	f
23.8	d	$^{3}J_{CF}$ 4.6	-	c
32.5	s	-	-	b
33.5	s	-	-	a
35.9	d	$^{2}J_{CF}$ 20.6	-	d
90.7	d	$^{1}J_{CF}$ 164.9	-	e
9.34	d	$^{3}J_{CF}$ 5.7	-	l
28.1	d	$^{2}J_{CF}$ 21.0	-	i or k
28.4	d	$^{3}J_{CF}$ 3.8	-	h
33.2	d	$^{2}J_{CF}$ 20.9	-	i or k
33.6	s	-	-	g
94.8	d	$^{1}J_{CF}$ 168.3	-	j

No. 25 Decyltrimethylsilane (85)

$$\overset{a}{(CH_3)_3}\overset{b}{Si}\overset{c}{CH_2}\overset{d}{CH_2}\overset{e}{CH_2}\overset{f}{CH_2}\overset{g}{CH_2}\overset{h}{CH_2}\overset{i}{CH_2}\overset{j}{CH_2}\overset{k}{CH_3}$$

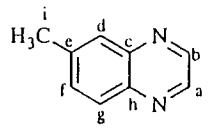
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^1H				
0.02	s	-	9	a
0.52	m	-	2	b
0.93	t	$^3J_{HH}$ 7.0	3	k
1.31	br s	-	16	c-j
^{13}C				
0.4	s	-	-	a
16.2	s	-	-	k
18.8	s	-	-	b
24.0	s	-	-	one of c-j
26.0	s	-	-	one of c-j
31.5	s	-	-	one of c-j
31.5	s	-	-	one of c-j
31.7	s	-	-	one of c-j
31.8	s	-	-	one of c-j
34.0	s	-	-	one of c-j
35.8	s	-	-	one of c-j

No. 26 Hexanenitrile (87)

$$\overset{a}{CH_3}\overset{b}{CH_2}\overset{c}{CH_2}\overset{d}{CH_2}\overset{e}{CH_2}\overset{f}{CN}$$

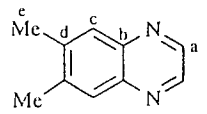
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^1H				
0.91	t	$^3J_{HH}$ 6.8	3	a
1.36	m	-	2	b, c or d
1.41	m	-	2	b, c or d
1.64	m	-	2	b, c or d
2.33	t	$^3J_{HH}$ 7.2	2	e
^{13}C				
13.7	s	-	-	a
17.1	s	-	-	e
21.8	s	-	-	b, c or d
25.0	s	-	-	b, c or d
30.7	s	-	-	b, c or d
119.9	s	-	-	f

No. 27 6-Methylquinoxaline (88)



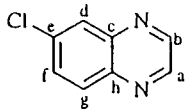
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^1H				
2.51	s	-	3	i
7.51	dd	$^3J_{HH}$ 8.8 $^4J_{HH}$ 2.0	1	f
7.79	s	-	1	d
7.91	d	$^3J_{HH}$ 8.8	1	g
8.68 and 8.72	AB	J_{AB} 2.0	2	b and a respec.
^{13}C				
21.6	s	-	-	i
128.1	s	-	-	d
128.8	s	-	-	g
132.2	s	-	-	f
140.4	s	-	-	e
141.3	s	-	-	h
142.9	s	-	-	c
143.9	s	-	-	a
144.7	s	-	-	b

No. 28 6,7-Dimethylquinoxaline (89)



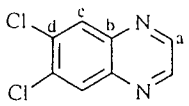
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^1H				
2.42	s	-	3	e
7.76	s	-	1	c
8.66	s	-	1	a
^{13}C				
20.3	s	-	-	e
128.3	s	-	-	c
140.6	s	-	-	d
141.9	s	-	-	b
143.9	s	-	-	a

No. 29 6-Chloroquinoxaline (90)



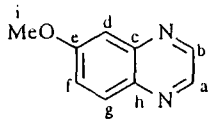
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{1}H				
7.67	dd	$^{3}J_{HH}$ 9.0 $^{4}J_{HH}$ 2.4	1	f
8.00	d	$^{3}J_{HH}$ 9.0	1	g
8.06	d	$^{4}J_{HH}$ 2.4	1	d
8.78 and 8.79	AB	J_{AB} 1.6	2	a and b respec.
^{13}C				
128.4	s	-	-	d
130.8	s	-	-	f
131.2	s	-	-	g
136.0	s	-	-	e
141.5	s	-	-	h
143.2	s	-	-	c
145.0	s	-	-	a
145.7	s	-	-	b

No. 30 6,7-Dichloroquinoxaline (91)



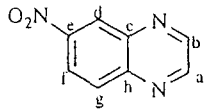
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{1}H				
8.25	s	-	1	c
8.85	s	-	1	a
^{13}C				
130.2	s	-	-	c
134.9	s	-	-	d
141.7	s	-	-	b
145.9	s	-	-	a

No. 31 6-Methoxyquinoxaline (92)



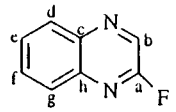
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^1H				
3.95	s		3	i
7.35	d	$^4J_{HH}$ 2.8	1	d
7.41	dd	$^3J_{HH}$ 9.2 $^4J_{HH}$ 2.8	1	f
7.96	d	$^3J_{HH}$ 9.2	1	g
8.67 and 8.74	AB	J_{AB} 2.0	2	a and b respec.
^{13}C				
55.8	s	-	-	i
106.6	s	-	-	d
123.5	s	-	-	f
130.3	s	-	-	g
139.2	s	-	-	h
142.3	s	-	-	a
144.6	s	-	-	c
144.8	s	-	-	b
160.7	s	-	-	e

No. 32 6-Nitroquinoxaline (93)



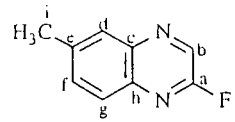
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^1H				
8.27	d	$^3J_{HH}$ 9.2	1	g
8.57	dd	$^3J_{HH}$ 9.2 $^4J_{HH}$ 2.8	1	f
9.02 and 9.03	AB	J_{AB} 1.6	1	a and b respec.
9.04	d	$^4J_{HH}$ 2.8	1	d
^{13}C				
123.5	s	-	-	f
126.0	s	-	-	d
131.4	s	-	-	g
141.9	s	-	-	c
145.3	s	-	-	h
147.0	s	-	-	b
147.7	s	-	-	a
147.8	s	-	-	e

No. 33 2-Fluoroquinoxaline (95)



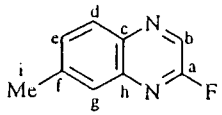
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-74.36	d	$^{3}J_{HF}$ 7.5	-	-
^{1}H				
7.73	t	$^{3}J_{HH}$ 6.8	1	e or f
7.77	t	$^{3}J_{HH}$ 6.8	1	e or f
7.93	d	$^{3}J_{HH}$ 8.0	1	d
8.13	d	$^{3}J_{HH}$ 8.0	1	g
8.67	d	$^{3}J_{HF}$ 7.6	1	b
^{13}C				
128.1	s	-	-	d
129.1	s	-	-	g and e or f
131.3	s	-	-	e or f
136.1	d	$^{2}J_{CF}$ 42.8	-	b
139.4	d	$^{3}J_{CF}$ 10.7	-	h
141.2	s	-	-	c
156.3	d	$^{1}J_{CF}$ 256.0	-	a

No. 34 2-Fluoro-6-methylquinoxaline (96A)



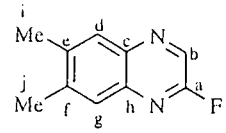
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-76.67	d	$^{3}J_{HF}$ 7.53	-	-
^{1}H				
2.59	s	-	3	i
7.63	dd	$^{3}J_{HH}$ 8.3 $^{4}J_{HH}$ 2.0	1	f
7.78	d	$^{3}J_{HH}$ 8.3	1	g
7.92	br s	-	1	d
8.65	d	$^{3}J_{HF}$ 8.0	1	b
^{13}C				
21.6	s	-	-	i
127.6	s	-	-	g
128.1	s	-	-	d
133.6	s	-	-	f
134.6	d	$^{2}J_{CF}$ 43.0	-	b
137.6	d	$^{3}J_{CF}$ 13.7	-	h
139.7	s	-	-	c
141.3	s	-	-	e
156.2	d	$^{1}J_{CF}$ 255.1	-	a

No. 35 2-Fluoro-7-methylquinoxaline (96B)



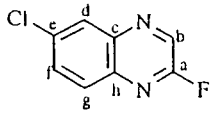
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-75.45	d	$^{3}J_{HF}$ 7.53	-	-
^{1}H				
2.59	s	-	3	i
7.58	dd	$^{3}J_{HH}$ 8.4 $^{4}J_{HH}$ 1.6	1	e
7.72	br s	-	1	g
8.03	d	$^{3}J_{HH}$ 8.3	1	d
8.62	d	$^{3}J_{HF}$ 8.0	1	b
^{13}C				
21.8	s	-	-	i
127.1	s	-	-	g
128.6	s	-	-	d
131.4	s	-	-	e
135.8	d	$^{2}J_{CF}$ 42.3	-	b
137.6	d	$^{3}J_{CF}$ 13.7	-	h
139.7	s	-	-	c
142.3	s	-	-	f
156.7	d	$^{1}J_{CF}$ 255.1	-	a

No. 36 2-Fluoro-6,7-dimethylquinoxaline (97)



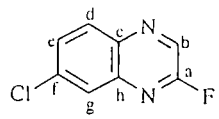
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-83.90	br s	-	-	-
^{1}H				
2.42	s	-	6	i and j
7.63	s	-	1	d
7.81	s	-	1	g
8.52	d	$^{3}J_{HF}$ 6.4	1	b
^{13}C				
20.2	s	-	-	i or j
20.4	s	-	-	i or j
127.2	s	-	-	d
128.2	s	-	-	g
134.7	d	$^{2}J_{CF}$ 42.8	-	b
138.2	d	$^{3}J_{CF}$ 10.8	-	h
139.5	d	$^{4}J_{CF}$ 3.1	-	c
140.2	s	-	-	e or f
142.2	s	-	-	e or f
156.4	d	$^{1}J_{CF}$ 255.3	-	a

No. 37 6-Chloro-2-fluoroquinoxaline (98A)



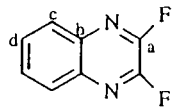
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-74.29	d	$^{3}J_{HF}$ 7.6	-	-
^{1}H				
7.75	dd	$^{3}J_{HH}$ 8.8	1	f
		$^{4}J_{HH}$ 2.4		
7.91	d	$^{3}J_{HH}$ 8.8	1	g
8.15	d	$^{4}J_{HH}$ 2.4	1	d
8.71	d	$^{3}J_{HH}$ 7.6	1	b
^{13}C				
128.5	s	-	-	d
129.5	s	-	-	g
132.6	s	-	-	f
135.3	s	-	-	e
137.4	d	$^{2}J_{CF}$ 42.5	-	b
137.7	d	$^{3}J_{CF}$ 9.1	-	h
141.8	s	-	-	c
156.7	d	$^{1}J_{CF}$ 257.2	-	a

No. 38 7-Chloro-2-fluoroquinoxaline (98B)



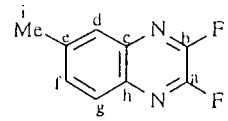
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-73.33	d	$^{3}J_{HF}$ 7.5	-	-
^{1}H				
7.71	dd	$^{3}J_{HH}$ 8.8	1	e
		$^{4}J_{HH}$ 2.4		
7.95	d	$^{4}J_{HH}$ 2.4	1	g
8.09	d	$^{3}J_{HH}$ 8.8	1	d
8.68	d	$^{3}J_{HF}$ 8.0	1	b
^{13}C				
127.4	s	-	-	g
130.6	s	-	-	d and e
135.3	s	-	-	f
136.5	d	$^{2}J_{CF}$ 42.5	-	b
138.2	d	$^{3}J_{CF}$ 11.0	-	h
140.1	s	-	-	c
157.2	d	$^{1}J_{CF}$ 257.9	-	a

No. 39 2,3-Difluoroquinoxaline (100)



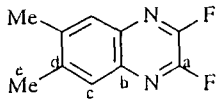
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-79.14	s	-	-	-
^{1}H				
7.79	m	-	1	c or d
7.99	m	-	1	c or d
^{13}C				
127.8	s	-	-	c or d
130.4	s	-	-	c or d
138.3	m	-	-	b
146.1	dd	$^{1}J_{CF}$ 263.1 $^{2}J_{CF}$ 39.5	-	a

No. 40 2,3-Difluoro-6-methylquinoxaline (101)



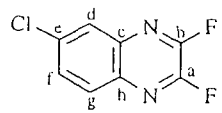
Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-83.20 and -84.56	AB	$^{3}J_{FF}$ 30.5	-	-
^{1}H				
2.59	s	-	3	i
7.59	dd	$^{3}J_{HH}$ 8.8 $^{4}J_{HH}$ 1.4	1	f
7.74	s	-	1	d
7.85	d	$^{3}J_{HH}$ 8.4	1	g
^{13}C				
21.7	s	-	-	i
126.9	s	-	-	d
127.2	s	-	-	g
132.4	s	-	-	f
136.5	d	$^{3}J_{CF}$ 6.1	-	c or h
138.4	d	$^{3}J_{CF}$ 6.1	-	c or h
141.1	s	-	-	e
145.7	dd	$^{1}J_{CF}$ 257.6 $^{2}J_{CF}$ 35.8	-	a or b
146.1	dd	$^{1}J_{CF}$ 257.6 $^{2}J_{CF}$ 35.8	-	a or b

No. 41 2,3-Difluoro-6,7-dimethylquinoxaline (102)



Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-85.05	s	-	-	-
^{1}H				
2.47	s	-	3	e
7.70	s	-	1	c
^{13}C				
20.3	s	-	-	e
127.0	s	-	-	c
136.9	t	$^{3}J_{CF}$ 5.3 $^{4}J_{CF}$ 5.3	-	b
140.9	s	-	-	d
145.7	dd	$^{1}J_{CF}$ 249.5 $^{2}J_{CF}$ 39.1	-	a

No. 42 2,3-Difluoro-6-chloroquinoxaline (103)



Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)	Relative Intensity	Assignment
^{19}F				
-80.88	d	$^{3}J_{FF}$ 29.7	-	a or b
-82.00	d	$^{3}J_{FF}$ 30.1	-	a or b
^{1}H				
7.74	dd	$^{3}J_{HH}$ 8.8 $^{4}J_{HH}$ 2.0	1	f
7.92	d	$^{3}J_{HH}$ 8.8	1	g
7.98	d	$^{4}J_{HH}$ 2.0	1	d
^{13}C				
127.0	s	-	-	d
128.9	s	-	-	g
131.4	s	-	-	f
136.4	s	-	-	e
136.9	d	$^{3}J_{CF}$ 7.1	-	c or h
138.8	d	$^{3}J_{CF}$ 7.1	-	c or h
146.2	dd	$^{1}J_{CF}$ 258.8 $^{2}J_{CF}$ 35.3	-	a or b
146.8	dd	$^{1}J_{CF}$ 259.9 $^{2}J_{CF}$ 35.3	-	a or b

Appendix 2: Mass Spectra

All spectra were determined using electron impact (EI) ionisation except spectrum no. 20 which was determined using chemical ionisation (ammonia).

No. 1 Fluorocyclohexane (**37**)

No. 2 *cis*-9-Fluorodecalin (**47**)

No. 3 *trans*-9-Fluorodecalin (**49**)

No. 4 *trans*-1- and 2-Fluorodecalin (**63A-D**)

No. 5 *cis*-1- and 2-Fluorodecalin (**64A-D**)

No. 6 *exo*- and *endo*-2-Fluoronorbornane (**43A, B**)

No. 7 1-Fluoroadamantane (**44**)

No. 8 1-Fluoro-2-methylheptane (**51A**) and 1-Fluoro-6-methylheptane (**51B**)

No. 9 2-, 3-, 4-, and 5-Fluorodecane (**53A-D**)

No. 10 3β-Acetoxy-5α-androstanone (**55**)

No. 11 N-(1-Adamantyl)acetamide (**65**)

No. 12 N-(1-Adamantyl)propylamide (**66**)

No. 13 N-(Cyclohexyl)acetamide (**67**)

No. 14 N-(*trans*-9-Decalyl)acetamide (**68**)

No. 15 N-(*exo*-2-Norbornyl)acetamide (**69**)

No. 16 1-Aminoadamantane (**70**)

No. 17 1-Hydroxyadamantane (**71**)

No. 18 1-Ethoxyadamantane (**72**)

No. 19 Methyl 3-fluorovalerate (**74A**) and Methyl 4-fluorovalerate (**74B**)

No. 20 Methyl 3-, 4-, 5-, and 6-fluoroenanthate (**76A-D**)

No. 21 Dimethyl 3-fluoropimelate (**79A**) and Dimethyl 4-fluoropimelate (**79B**)

No. 22 1-Chloro-4-fluorohexane (**84B**) and 1-Chloro-5-fluorohexane (**84C**)

No. 23 1-Bromo-4-fluorohexane (**82B**) and 1-Bromo-5-fluorohexane (**82C**)

No. 24 Decyltrimethylsilane (**85**)

No. 25 Hexanenitrile (**87**)

No. 26 6-Methylquinoxaline (**88**)

No. 27 6,7-Dimethylquinoxaline (**89**)

No. 28 6-Chloroquinoxaline (**90**)

No. 29 6,7-Dichloroquinoxaline (**91**)

No. 30 6-Methoxyquinoxaline (**92**)

No. 31 6-Nitroquinoxaline (**93**)

No. 32 2-Fluoroquinoxaline (**95**)

No. 33 2-Fluoro-6-methylquinoxaline (**96A**) and

2-Fluoro-7-methylquinoxaline (**96B**)

No. 34 2-Fluoro-6,7-dimethylquinoxaline (**97**)

No. 35 6-Chloro-2-fluoroquinoxaline (**98A**) and
7-Chloro-2-fluoroquinoxaline (**98B**)

No. 36 2,3-Difluoroquinoxaline (**100**)

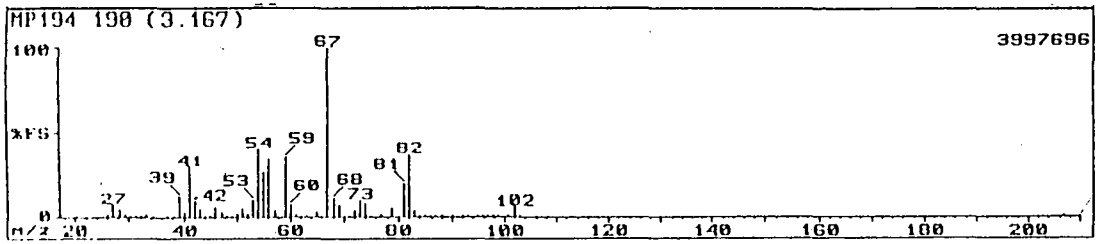
No. 37 2,3-Difluoro-6-methylquinoxaline (**101**)

No. 38 2,3-Difluoro-6,7-dimethylquinoxaline (**102**)

No. 39 2,3-Difluoro-6-chloroquinoxaline (**103**)

No. 1 Fluorocyclohexane (37)

$M^{+\bullet} = 102$

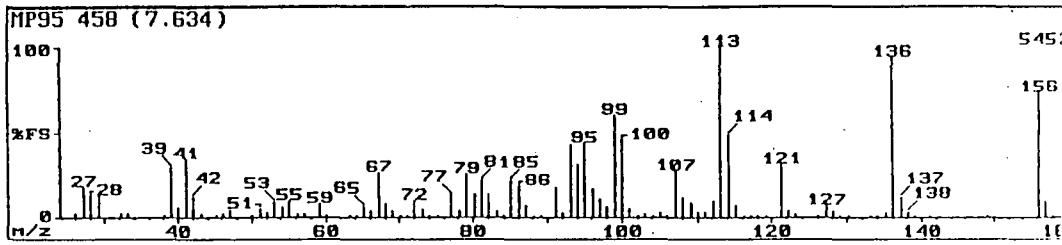


Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.01	44	0.36	62	0.44	84	0.22
26	1.50	45	1.08	63	0.93	85	1.23
27	6.86	46	5.40	65	2.61	86	0.13
28	4.41	47	2.43	67	100.00	87	0.76
29	2.36	48	0.12	68	11.07	88	0.05
30	0.06	49	0.36	69	6.86	90	0.02
31	0.23	50	2.41	70	1.01	92	0.03
32	0.13	51	4.89	71	0.77	93	0.03
33	1.53	52	1.66	72	3.51	95	0.28
34	0.01	53	9.73	73	9.84	96	0.19
37	0.37	54	39.34	74	7.68	97	0.32
38	1.19	55	26.23	75	0.56	98	0.05
39	11.37	56	34.02	77	2.33	99	0.12
40	2.64	57	4.23	79	4.53	101	0.28
41	29.10	59	34.84	81	18.95	102	5.56
42	8.40	60	6.35	82	36.48	103	0.30
43	5.33	61	1.72	83	3.41	207	0.01

B3

No. 2 *cis*-9-Fluorodecalin (47)

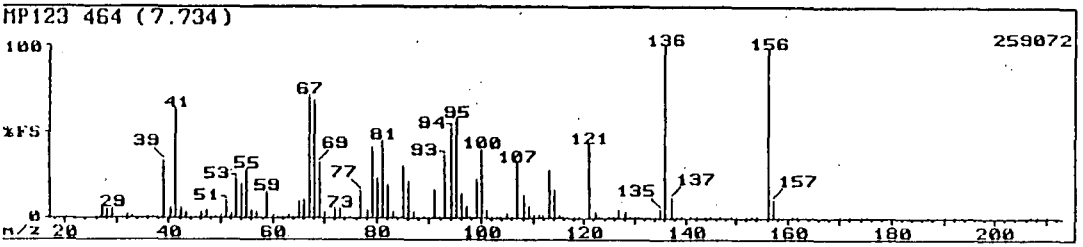
$M^{+\bullet} = 156$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
26	1.74	63	0.74	89	0.67	115	6.57
27	17.37	64	0.61	91	17.84	116	0.56
28	12.91	65	5.90	92	2.82	117	1.03
29	12.91	66	3.46	93	42.25	118	0.74
32	1.57	67	25.82	94	30.99	119	0.85
33	2.23	68	8.22	95	43.66	121	31.46
38	1.17	69	4.20	96	16.43	122	3.81
39	28.87	70	1.29	97	10.56	123	1.70
40	5.52	71	1.27	98	6.19	126	1.04
41	34.27	72	9.98	99	60.56	127	6.78
42	11.62	73	4.72	100	45.54	128	4.11
43	1.64	74	0.67	101	4.72	129	1.16
45	0.54	75	0.36	102	0.61	130	0.56
46	2.29	77	12.21	103	1.56	133	0.73
47	3.64	78	3.70	104	0.73	134	0.65
50	1.19	79	25.23	105	3.17	135	3.05
51	5.13	80	13.15	106	1.07	136	93.90
52	2.64	81	21.83	107	27.23	137	11.85
53	8.92	82	13.73	108	11.74	138	3.37
54	5.40	83	3.73	109	9.04	139	0.89
55	9.51	84	1.44	110	3.32	141	0.92
56	1.87	85	21.13	111	2.67	149	0.73
57	2.08	86	18.19	112	9.62	156	74.18
59	7.98	87	6.63	113	100.00	157	9.39
60	1.35	88	0.48	114	48.83	158	0.73

No. 3 *trans*-9-Fluorodecalin (49)

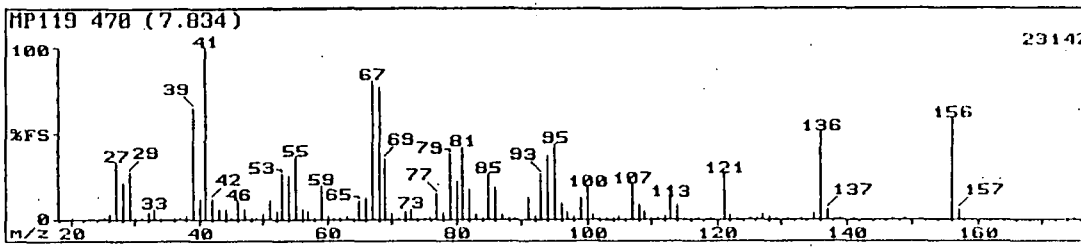
$M^{+\bullet} = 156$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.07	61	1.03	96	14.92	133	0.48
26	0.42	62	0.51	97	6.62	134	0.32
27	5.76	63	1.75	98	1.30	135	5.16
28	4.72	64	0.80	99	22.73	136	100.00
29	5.85	65	9.39	100	28.46	137	11.36
30	0.17	66	10.28	101	4.55	138	1.20
31	0.15	67	71.15	102	0.64	139	0.72
32	2.57	68	68.38	103	0.80	141	0.34
33	1.63	69	31.62	104	0.27	142	0.18
36	0.13	70	3.85	105	2.52	144	0.20
37	0.28	71	1.37	106	0.61	145	0.16
38	1.07	72	6.15	107	32.41	147	0.20
39	32.81	73	5.83	108	13.93	149	0.27
40	6.52	74	0.73	109	7.11	150	0.11
41	62.85	75	0.69	110	1.61	152	0.39
42	7.11	77	15.22	111	2.03	153	0.20
43	4.10	78	4.62	112	1.98	154	0.26
44	1.42	79	40.32	113	28.06	156	97.63
45	1.20	80	23.32	114	16.21	157	10.97
46	4.03	81	45.06	115	1.83	158	0.73
47	4.45	82	19.07	116	0.28	161	0.12
48	0.21	83	3.83	117	0.45	162	0.16
49	0.43	84	0.78	118	0.96	170	0.22
50	2.10	85	30.43	119	0.43	172	0.32
51	9.29	86	21.25	121	42.69	174	1.10
52	3.04	87	3.93	122	4.35	175	0.26
53	22.73	88	0.47	123	0.59	190	0.21
54	20.55	89	0.54	125	0.52	192	0.35
55	28.06	90	0.28	126	0.78	207	0.60
56	4.87	91	16.50	127	4.45	208	0.11
57	3.63	92	1.27	128	4.03	210	0.19
58	0.48	93	35.97	129	0.83		
59	15.71	94	50.99	130	0.31		
60	1.78	95	57.71	131	0.30		

No. 4 *trans*-1- and 2-Fluorodecalin (63A-D)

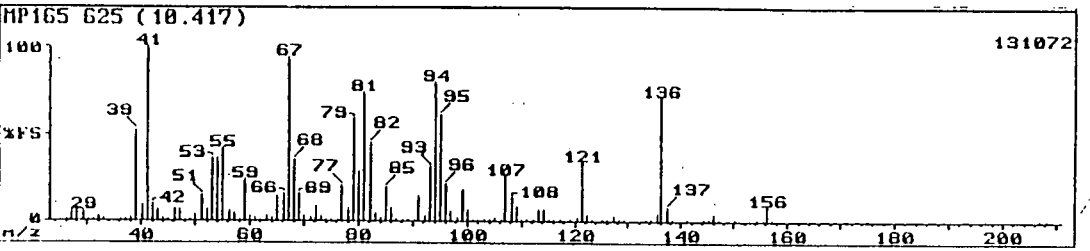
$M^{+\bullet} = 156$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.19	55	35.84	85	26.22	116	0.19
25	0.18	56	6.17	86	18.25	117	0.15
26	2.43	57	4.54	87	2.88	119	0.34
27	32.74	58	0.88	88	0.34	121	25.77
28	21.24	59	19.69	89	0.37	122	2.63
29	27.21	60	2.27	91	12.50	123	0.32
30	0.75	61	1.12	92	1.99	125	0.20
31	0.43	62	0.55	93	25.88	126	0.21
32	4.23	63	1.96	94	37.17	127	2.65
33	5.48	64	0.72	95	43.36	128	2.05
34	0.12	65	10.62	96	10.18	129	0.29
36	0.22	66	12.28	97	4.48	131	0.11
37	0.55	67	80.53	98	1.51	133	0.13
38	2.24	68	76.99	99	12.50	135	1.46
39	64.16	69	34.51	100	18.58	136	50.00
40	11.62	70	3.98	101	2.88	137	5.42
41	100.00	71	1.42	102	0.36	138	0.44
42	11.84	72	4.87	103	0.71	139	0.21
43	6.25	73	5.37	104	0.29	141	0.28
44	5.95	74	0.67	105	1.65	147	0.09
45	1.40	75	0.53	106	0.50	149	0.12
46	10.62	76	0.38	107	20.80	154	0.13
47	5.81	77	14.27	108	9.07	156	58.41
48	0.20	78	4.34	109	4.56	157	6.06
49	0.22	79	37.61	110	0.80	158	0.38
50	2.54	80	22.01	111	1.01	174	0.41
51	10.29	81	41.59	112	1.68	175	0.08
52	5.20	82	17.92	113	13.05		
53	26.66	83	3.35	114	8.52		
54	25.33	84	1.37	115	1.22		

No. 5 *cis*-1- and 2-Fluorodecalin (64A-D)

$M^{+\bullet} = 156$

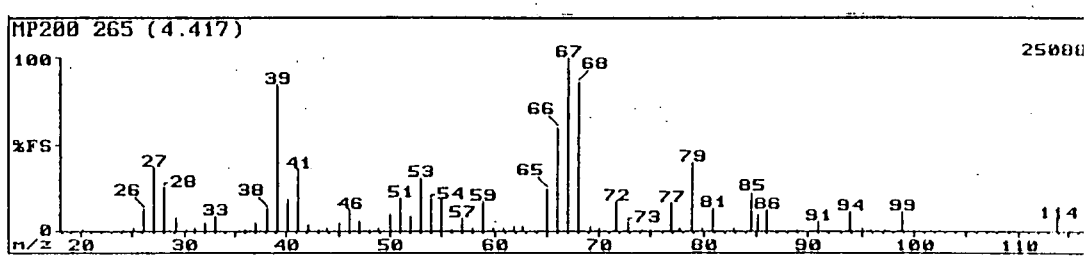


Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
26	0.33	58	0.95	88	0.18	119	0.33
27	5.76	59	24.02	89	0.52	120	2.17
28	6.15	60	2.71	90	0.56	121	14.38
29	6.30	61	1.49	91	14.84	122	3.52
30	0.20	62	0.81	92	3.13	123	0.42
31	0.12	63	3.02	93	30.86	125	0.47
32	2.91	64	1.62	94	79.69	126	0.74
33	2.09	65	14.45	95	60.16	127	2.71
36	0.15	66	15.43	96	20.90	128	1.04
37	0.38	67	94.53	97	6.20	129	0.14
38	1.54	68	34.77	98	2.27	133	0.16
39	51.56	69	15.63	99	18.16	134	0.31
40	10.16	70	2.47	100	7.03	135	4.83
41	100.00	71	1.81	101	1.00	136	71.09
42	9.67	72	9.08	102	0.37	137	7.67
43	6.74	73	2.84	103	0.42	138	0.50
44	1.61	74	1.12	104	0.27	141	0.55
45	1.33	75	0.99	105	2.36	144	0.22
46	7.03	76	1.04	106	1.18	145	0.49
47	6.79	77	20.12	107	26.56	146	3.91
48	0.24	78	7.76	108	13.87	147	0.52
49	0.20	79	58.59	109	8.69	150	0.10
50	3.71	80	29.30	110	0.98	154	0.17
51	14.84	81	73.44	111	0.92	156	0.30
52	7.03	82	44.34	112	1.10	156	8.64
53	35.74	83	5.18	113	6.79	157	0.93
54	36.72	84	1.95	114	7.08	207	0.32
55	41.41	85	19.14	115	1.25	208	0.06
56	6.10	86	7.91	116	0.23		
57	5.13	87	1.44	117	0.21		

B5

No. 6 *exo*- and *endo*-2-Fluoronorbornane (43A, B)

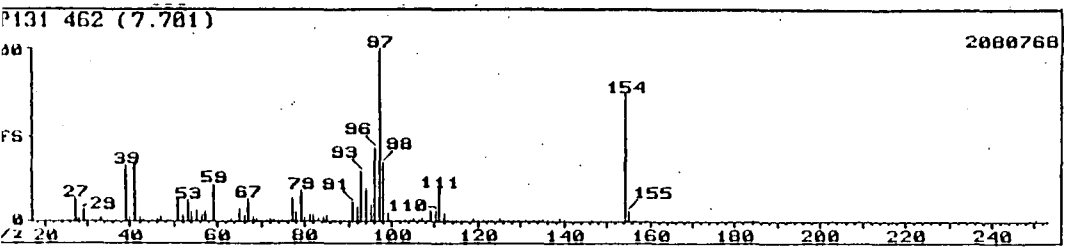
$M^{+\bullet} = 114$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.66	43	0.90	61	1.47	83	2.42
24	0.64	44	2.40	62	3.11	85	11.94
25	1.94	45	4.41	63	3.32	85	9.49
26	12.86	46	12.65	65	24.69	86	13.06
27	37.14	47	5.89	66	59.59	89	0.36
28	25.71	48	0.42	67	100.00	91	6.25
29	8.06	49	1.56	68	85.31	94	11.53
30	0.32	50	9.59	69	2.70	95	1.68
31	2.02	51	19.80	70	1.50	96	0.54
32	4.95	52	8.78	72	17.04	97	0.56
33	8.78	53	30.61	73	5.10	99	11.33
36	0.64	54	18.57	74	0.64	100	0.53
37	4.74	55	18.57	75	0.57	109	0.33
38	12.35	56	1.35	77	16.73	114	8.16
39	84.08	57	7.76	78	2.24	115	0.30
40	18.88	58	1.81	79	40.00		
41	35.51	59	17.65	80	2.12		
42	4.34	60	1.99	81	13.37		

No. 7 1-Fluoroadamantane (44)

$M^{+\bullet} = 154$

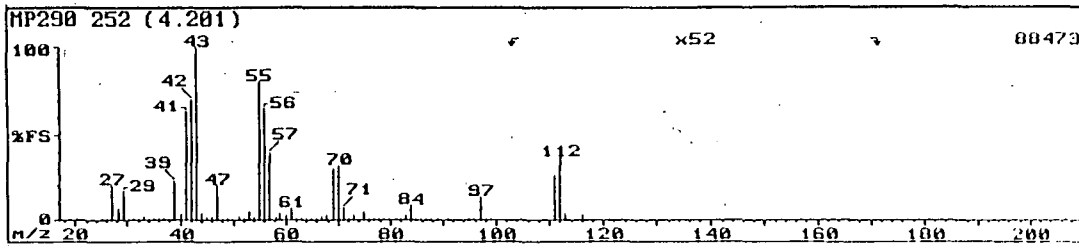


Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.09	57	5.71	87	0.43	116	0.13
24	0.01	59	11.07	88	0.07	117	0.30
26	0.59	60	0.96	89	0.32	119	2.04
27	13.98	61	0.48	90	0.81	120	0.22
28	3.35	62	0.78	91	10.78	121	0.12
29	6.74	63	2.10	92	8.61	122	0.05
30	0.15	64	1.30	93	29.53	123	0.35
31	0.23	65	7.38	94	19.29	125	1.55
32	0.30	66	4.13	95	9.84	126	0.45
33	2.78	67	13.78	96	42.72	127	0.08
35	0.02	68	2.68	97	100.00	128	0.07
36	0.09	69	2.09	98	34.25	129	0.03
37	0.21	70	1.02	99	5.27	131	0.10
39	33.27	71	0.61	100	0.64	133	0.86
40	2.85	72	1.93	101	0.20	134	1.03
41	32.87	73	1.67	102	0.18	135	0.63
42	2.51	74	0.35	103	0.50	136	0.07
43	2.04	75	0.80	104	0.27	137	0.04
44	0.29	76	0.98	105	2.14	139	1.82
45	0.94	77	13.58	106	0.64	140	0.14
46	1.82	78	5.71	107	2.28	146	0.02
47	2.51	79	18.50	108	0.80	154	74.80
49	0.11	80	3.20	109	5.61	155	6.30
51	12.16	81	3.44	110	5.76	156	0.18
52	3.89	82	3.64	111	19.09	184	0.02
53	12.80	83	2.24	112	4.43	250	0.03
54	5.81	84	2.81	113	1.40		
55	6.94	85	3.84	114	0.15		
56	3.74	86	1.09	115	0.41		

B6

No. 8 1-Fluoro-2-methylheptane (51A) and 1-Fluoro-6-methylheptane (51B)

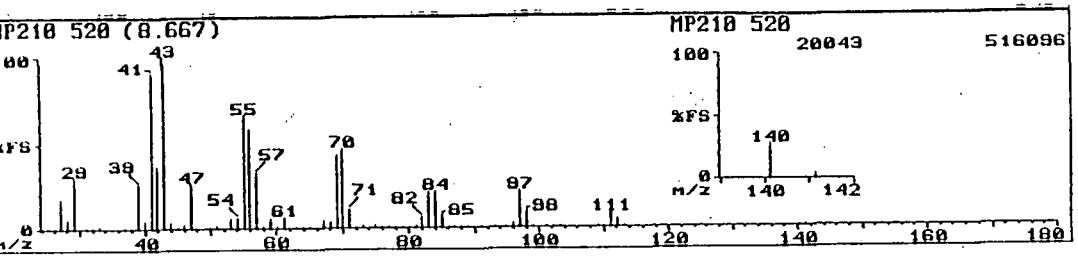
$M^{+\bullet} = 132$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.09	44	3.99	64	0.09	84	8.91
25	0.05	45	1.48	65	0.71	85	0.92
26	1.06	46	2.29	66	0.22	86	0.10
27	20.72	47	20.49	67	1.74	87	0.20
28	6.89	48	0.54	68	2.66	88	1.12
29	16.78	49	0.11	69	30.09	89	0.55
30	0.44	50	0.98	70	32.41	91	0.07
31	0.13	51	1.81	71	7.20	95	0.19
32	1.19	52	0.57	72	0.54	96	0.28
33	1.83	53	4.54	73	2.86	97	13.89
34	0.03	54	1.67	74	0.36	98	1.12
35	0.04	55	80.56	75	5.15	99	0.07
36	0.16	56	65.28	76	0.27	111	0.51
37	0.27	57	38.43	77	0.35	112	0.71
38	1.06	58	1.81	78	0.08	113	0.08
39	21.99	59	3.99	79	0.40	116	0.05
40	4.08	60	2.60	80	0.06	207	0.12
41	63.43	61	6.60	81	0.96		
42	70.37	62	0.41	82	0.20		
43	100.00	63	0.41	83	3.07		

No. 9 2-, 3-, 4-, and 5-Fluorodecane (53A-D)

$M^{+\bullet} = 160$

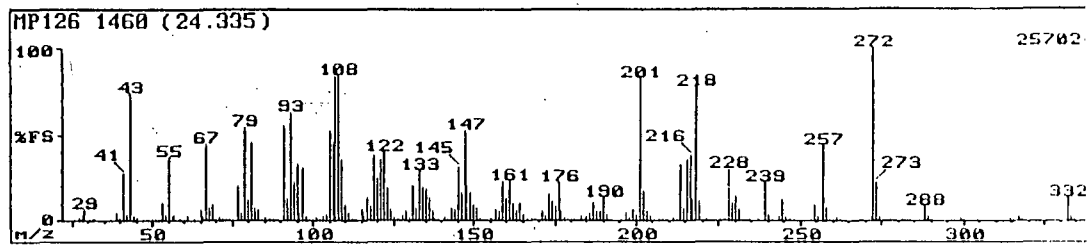


Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
26	0.91	50	0.47	70	46.23	91	0.14
27	17.66	51	1.70	71	11.11	93	0.07
28	5.95	52	0.69	72	0.93	95	0.39
29	29.96	53	5.80	73	2.42	96	2.88
30	0.78	54	5.90	74	1.17	97	21.63
31	0.09	55	65.87	75	2.00	98	8.48
32	0.65	56	57.94	76	0.13	99	0.72
33	1.60	57	31.94	77	0.53	101	0.05
37	0.20	58	1.50	78	0.12	102	0.06
38	0.73	59	5.80	79	0.60	103	0.11
39	25.00	60	2.10	80	0.12	109	0.06
40	5.06	61	6.40	81	2.07	110	0.76
41	90.48	62	0.29	82	6.30	111	8.83
42	16.71	63	0.22	83	20.83	112	4.96
43	100.00	64	0.08	84	21.63	113	0.40
44	3.47	65	0.83	85	6.75	125	0.17
45	1.12	66	0.56	86	0.49	140	1.10
46	2.52	67	5.01	87	0.38	141	0.14
47	25.99	68	4.27	88	0.45		
48	0.62	69	42.46	89	0.38		

B7

No. 10 3β-Acetoxy-5α-androstanone (55)

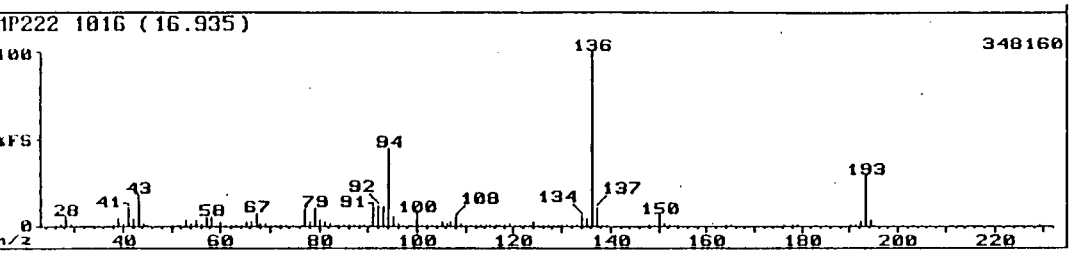
$M^{+\bullet} = 332$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
26	0.08	94	23.71	150	9.86	209	0.30
27	2.34	95	33.47	151	8.17	211	1.72
28	3.59	96	5.18	152	2.02	212	1.12
29	6.35	97	30.68	153	0.80	213	33.07
30	0.19	98	2.89	154	0.53	214	7.67
31	0.34	99	0.93	155	1.48	215	36.25
32	0.54	100	0.34	156	0.87	216	38.25
39	4.83	101	1.84	157	6.97	217	12.25
40	1.62	102	0.59	158	6.15	218	77.69
41	27.09	103	3.31	159	23.01	219	11.75
42	3.86	104	3.69	160	13.75	220	1.27
43	73.71	105	52.19	161	23.51	221	0.11
44	2.86	106	45.42	162	10.86	225	0.93
45	1.82	107	81.67	163	6.67	226	0.83
50	0.29	108	84.46	164	10.66	227	0.79
51	1.15	109	35.86	165	3.46	228	18.03
52	0.88	110	9.66	166	0.98	229	11.16
53	10.76	111	5.18	167	0.61	230	14.74
54	3.91	112	0.99	168	0.29	231	6.67
55	36.65	113	0.33	169	1.43	232	1.12
56	2.51	115	7.27	170	0.67	233	0.81
57	3.83	116	2.49	171	5.73	234	0.38
58	0.33	117	13.35	172	3.19	237	0.22
59	0.20	118	8.86	173	15.34	239	22.71
60	1.38	119	37.45	174	11.35	240	3.96
61	2.69	120	25.50	175	8.76	241	0.80
63	0.39	121	36.25	176	22.31	243	2.76
65	6.57	122	39.44	177	5.93	244	12.75
66	2.96	123	19.42	178	1.46	245	2.69
67	44.22	124	6.37	179	0.68	246	0.48
68	7.57	125	1.74	180	0.22	247	0.20
69	10.06	126	0.25	181	0.27	248	0.30
70	1.20	127	1.05	183	2.64	253	0.60
71	1.64	128	3.34	184	0.99	254	9.46
72	0.25	129	6.18	185	2.66	255	3.14
73	0.36	130	1.74	186	4.51	257	43.43
74	0.31	131	20.12	187	10.76	258	7.87
75	0.15	132	7.77	188	5.93	259	1.02
77	20.72	133	28.69	189	5.58	260	0.35
78	5.23	134	19.32	190	13.35	261	2.39
79	54.58	135	18.92	191	3.83	262	0.49
80	12.35	136	13.84	192	0.60	272	100.00
81	45.82	137	6.10	195	0.26	273	22.11
82	8.17	138	1.00	197	4.61	274	2.74
83	6.47	139	0.41	198	1.50	275	0.96
84	1.03	141	1.84	199	7.07	276	1.19
85	1.58	142	1.44	200	3.64	277	0.28
86	0.48	143	8.07	201	82.47	281	0.18
87	0.73	144	6.35	202	17.03	288	8.96
88	0.41	145	31.08	203	6.00	289	2.61
89	0.38	146	16.53	204	2.49	290	0.70
91	54.98	147	52.59	205	1.18	299	2.32

No. 11 N-(1-Adamantyl)acetamide (65)

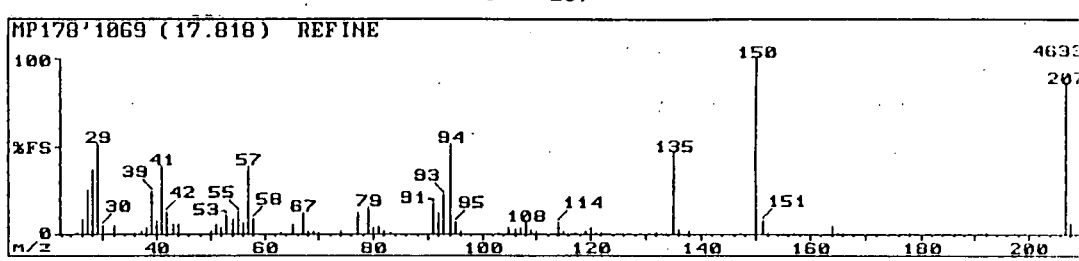
$M^{+\bullet} = 193$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
26	0.13	66	2.63	98	0.24	129	0.05
27	1.67	67	7.57	99	1.01	130	0.07
28	6.18	68	1.84	100	7.72	131	0.13
29	1.76	69	1.78	101	1.00	132	0.24
30	1.27	70	1.18	102	0.16	133	0.45
31	0.08	71	0.38	103	0.41	134	5.37
32	1.40	72	0.28	104	0.26	135	5.00
38	0.23	73	0.12	105	2.56	136	100.00
39	5.15	75	0.17	106	2.33	137	10.29
40	1.47	76	0.12	107	2.46	138	1.14
41	10.59	77	9.71	108	5.00	139	0.14
42	4.93	78	3.03	109	1.95	148	0.34
43	18.82	79	10.44	110	1.34	149	0.60
44	1.51	80	3.49	111	0.40	150	6.32
45	0.14	81	3.22	112	0.37	151	1.58
50	0.27	82	1.86	113	0.11	152	1.10
51	1.18	83	0.86	114	0.21	153	0.16
52	0.91	84	0.21	115	0.46	154	0.16
53	3.90	85	0.08	116	0.11	164	0.17
54	2.13	86	0.34	117	0.63	165	0.11
55	3.73	87	0.11	118	0.63	176	0.17
56	2.24	88	0.12	119	2.13	178	0.86
57	5.29	89	0.23	120	0.78	179	0.13
58	5.81	90	0.13	121	0.25	190	0.07
59	0.46	91	11.03	122	0.40	191	0.48
60	2.65	92	12.06	123	0.73	192	2.52
61	0.13	93	11.76	124	2.76	193	29.12
62	0.10	94	45.00	125	0.49	194	4.04
63	0.42	95	5.51	126	0.10	195	0.38
64	0.24	96	1.47	127	0.05	229	0.06
65	3.33	97	0.34	128	0.09		

No. 12 N-(1-Adamantyl)propylamide (66)

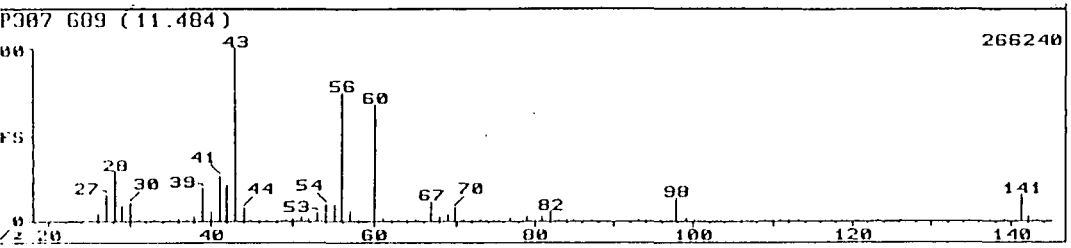
$M^{+\bullet} = 207$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
25	1.35	52	4.32	82	2.10	119	1.88
26	8.32	53	10.64	83	0.85	120	3.42
27	25.41	54	9.12	91	17.82	121	0.95
28	36.46	55	12.71	92	12.71	122	0.59
29	51.38	56	6.32	93	22.65	132	0.93
30	5.15	57	39.23	94	51.38	135	46.96
32	4.87	58	8.98	95	6.94	136	3.21
36	1.44	63	1.04	96	2.06	138	2.42
37	1.70	65	6.22	103	0.84	150	100.00
38	3.56	67	12.85	105	4.04	151	7.94
39	24.31	68	2.24	106	3.38	152	0.79
40	7.87	69	1.91	107	4.25	164	4.42
41	39.23	70	1.28	108	7.18	165	0.75
42	12.85	74	1.95	109	2.69	166	0.63
43	6.28	77	12.43	110	1.76	178	0.74
44	6.04	79	15.61	114	6.39	192	0.70
50	2.31	80	3.97	115	1.68	207	85.08
51	5.73	81	4.66	117	1.36	208	7.08

No. 13 N-(Cyclohexyl)acetamide (67)

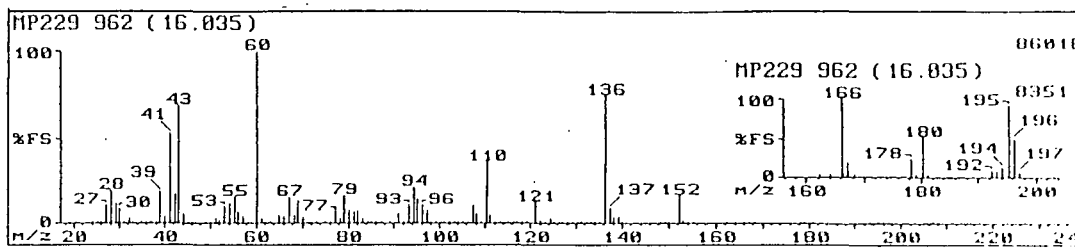
$M^{+\bullet}$ = 141



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.13	43	100.00	64	0.25	87	0.11
24	0.22	44	7.31	65	1.35	93	0.19
25	0.70	45	0.73	67	11.25	94	0.41
26	4.71	46	0.06	68	2.43	96	1.44
27	15.87	48	0.06	69	3.87	98	13.85
28	28.85	49	0.18	70	7.79	99	2.24
29	9.23	50	1.56	71	1.33	100	0.35
30	10.38	51	2.67	72	0.85	106	0.06
31	0.55	52	2.04	73	0.81	109	0.06
32	0.69	53	5.34	74	0.24	110	0.12
33	0.14	54	9.81	77	1.71	111	0.11
35	0.64	55	9.62	79	3.15	112	0.82
36	1.51	56	75.00	80	1.30	113	0.14
37	1.01	57	5.58	81	2.45	123	0.05
38	2.98	58	0.97	82	5.38	126	0.48
39	19.04	60	67.69	83	1.35	139	0.28
40	5.43	61	1.88	84	1.44	141	15.77
41	26.54	62	0.37	85	1.32	142	1.00
42	21.15	63	0.49	86	0.28	143	0.27

No. 14 N-(*trans*-9-Decalyl)acetamide (68)

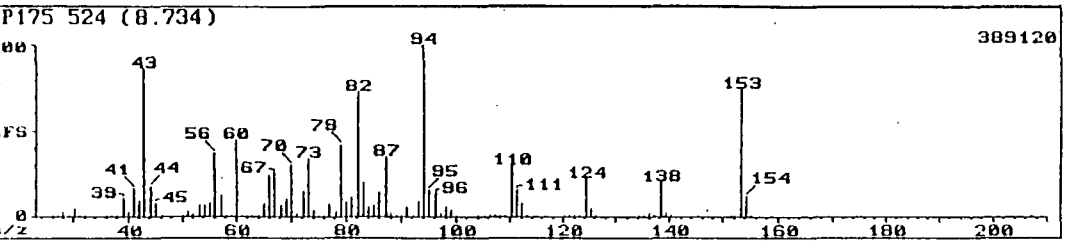
$M^{+\bullet}$ = 195



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.04	61	2.59	97	7.74	132	0.06
24	0.03	62	0.41	98	1.38	133	0.10
25	0.08	63	0.58	99	0.40	134	0.55
26	0.70	65	4.61	100	0.12	135	0.80
27	10.48	66	3.54	101	0.04	136	75.24
28	19.05	67	15.36	102	0.08	137	9.05
29	11.55	68	5.21	103	0.27	138	4.20
30	8.57	69	13.81	104	0.16	139	3.45
31	0.30	70	3.87	105	0.82	140	0.38
32	2.62	71	0.78	106	0.43	148	0.22
33	0.02	72	0.25	107	10.71	149	0.09
35	0.02	73	0.16	108	6.16	150	0.47
36	0.13	75	0.17	109	0.77	152	16.55
37	0.11	76	0.43	110	36.19	153	2.29
38	0.48	77	6.70	111	4.43	154	0.32
39	17.98	78	3.04	112	0.73	155	0.04
40	3.69	79	16.19	113	0.11	162	0.04
41	52.86	80	7.98	115	0.21	164	0.04
42	17.26	81	7.23	116	0.08	166	1.19
43	69.05	82	8.10	117	0.17	167	0.19
44	5.65	83	2.47	118	0.06	168	0.04
45	0.43	84	1.11	119	0.29	178	0.22
46	0.07	85	0.17	121	12.14	179	0.04
50	0.57	86	0.18	122	1.71	180	0.50
51	2.65	87	0.08	123	0.41	181	0.05
52	1.93	89	0.11	124	2.56	192	0.07
53	9.88	90	0.21	125	0.59	193	0.07
54	11.19	91	5.86	126	0.12	194	0.12
55	15.60	92	1.41	127	0.03	195	0.89
56	6.79	93	10.83	128	0.07	196	0.48
57	3.78	94	21.43	129	0.05	197	0.07
58	0.96	95	14.64	130	0.05	207	0.04
60	100.00	96	10.71	131	0.05		

No. 15 N-(*exo*-2-Norbornyl)acetamide (69)

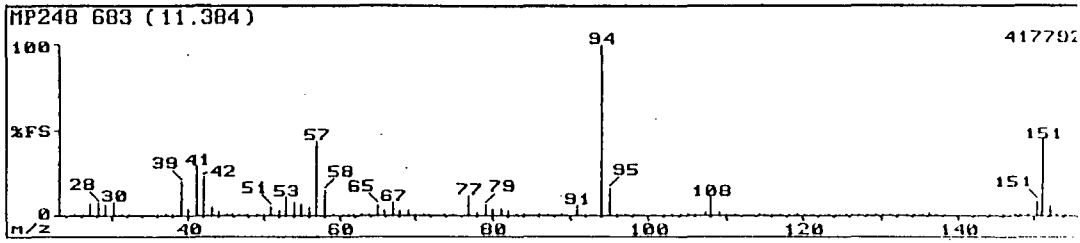
$M^{+\bullet}$ = 153



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
26	0.11	57	12.17	82	72.63	110	30.53
27	0.92	58	1.07	83	20.26	111	15.39
28	2.73	59	0.93	84	5.72	112	7.83
29	0.79	60	44.47	85	6.78	113	0.56
30	4.41	61	1.40	86	14.61	120	0.13
31	0.24	62	0.47	87	34.74	121	0.16
32	0.50	63	1.03	88	2.07	122	0.09
36	0.08	64	0.37	89	0.30	123	0.19
37	0.15	65	7.43	90	0.09	124	22.63
38	0.67	66	24.21	91	6.12	125	4.54
39	10.79	67	25.53	92	1.20	126	0.39
40	2.65	68	6.64	93	8.29	134	0.19
41	16.12	69	10.53	94	100.00	135	0.19
42	9.41	70	30.53	95	15.33	136	1.53
43	86.32	71	2.04	96	13.68	137	0.22
44	17.89	72	15.59	97	1.61	138	20.79
45	7.50	73	33.68	98	6.12	139	2.01
46	0.14	74	3.87	99	4.28	140	0.16
50	1.03	75	0.33	100	0.34	151	0.09
51	2.88	76	0.19	104	0.07	152	1.09
52	2.12	77	7.50	105	0.08	153	74.74
53	7.11	78	2.68	106	0.46	154	11.71
54	6.58	79	41.84	107	0.22	155	0.98
55	7.30	80	9.14	108	1.17	207	0.17
56	37.37	81	11.91	109	0.68		

No. 16 1-Aminoadamantane (70)

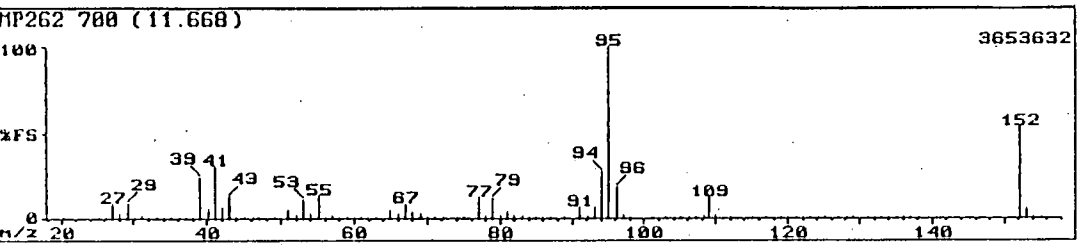
$M^{+\bullet}$ = 151



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
25	0.03	56	4.88	87	0.02	123	0.17
26	0.46	57	43.53	89	0.21	124	0.03
27	6.76	58	14.41	91	5.78	125	0.00
28	7.06	59	1.22	92	1.04	126	0.01
29	5.66	61	0.50	94	100.00	127	0.03
30	7.65	61	0.09	95	15.29	128	0.06
31	0.13	62	0.40	96	1.30	129	0.04
32	0.17	63	1.33	97	0.15	130	0.07
36	0.01	64	0.35	98	0.04	131	0.08
37	0.23	65	5.69	102	0.08	132	0.08
38	1.15	66	3.31	103	0.28	133	0.11
39	19.90	67	7.65	104	0.24	134	0.36
40	4.26	68	3.16	105	0.88	135	0.85
41	29.41	69	2.89	106	1.35	136	1.53
42	21.86	70	1.26	107	2.33	137	0.16
43	4.53	71	0.19	108	10.69	138	0.01
44	1.74	72	0.06	109	1.84	144	0.01
45	0.11	74	0.14	110	1.29	146	0.01
46	0.03	75	0.14	111	0.11	148	0.01
47	0.66	77	11.27	114	0.05	148	0.08
48	0.42	78	2.08	115	0.29	149	0.14
49	0.03	79	5.83	116	0.10	151	9.02
50	1.36	80	3.90	117	0.32	151	44.71
51	5.17	81	3.63	118	0.17	152	5.71
52	3.26	82	3.14	119	0.29	153	0.33
53	10.98	83	0.85	120	0.36	154	0.03
54	7.94	84	0.10	121	0.22		
55	6.86	86	0.02	122	0.48		

No. 17 1-Hydroxyadamantane (71)

$M^{+\bullet} = 152$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.01	51	4.88	81	4.34	112	0.04
25	0.03	52	2.30	82	1.96	115	0.31
26	0.50	53	10.65	83	1.60	116	0.11
27	8.97	54	2.91	84	0.37	117	0.22
28	2.61	55	14.01	85	0.06	118	0.07
29	8.30	56	1.15	86	0.04	119	0.23
30	0.25	57	1.99	87	0.04	120	0.03
31	2.19	58	1.25	89	0.25	121	0.10
32	0.30	59	0.64	91	7.12	122	0.06
33	0.03	60	0.12	92	1.79	123	0.26
34	0.01	61	0.20	93	6.36	124	0.15
35	0.01	62	0.23	94	27.58	125	0.03
36	0.03	63	1.01	95	100.00	127	0.03
37	0.24	65	4.43	96	18.50	128	0.05
38	1.16	66	2.63	97	1.99	129	0.03
39	24.33	67	8.63	98	0.21	131	0.05
40	5.35	68	3.76	101	0.05	132	0.02
41	31.39	69	2.66	102	0.13	133	0.07
42	6.50	70	1.07	103	0.38	134	0.16
43	12.78	71	0.28	104	0.19	135	0.85
44	0.70	72	0.03	105	0.97	136	0.11
45	0.67	74	0.10	106	0.27	137	0.74
46	0.05	75	0.11	107	1.11	138	0.08
47	0.11	77	12.67	108	2.16	152	52.91
48	0.06	78	1.88	109	12.22	153	5.49
49	0.07	79	11.43	110	1.85	154	0.39
50	1.35	80	1.57	111	0.37	155	0.04

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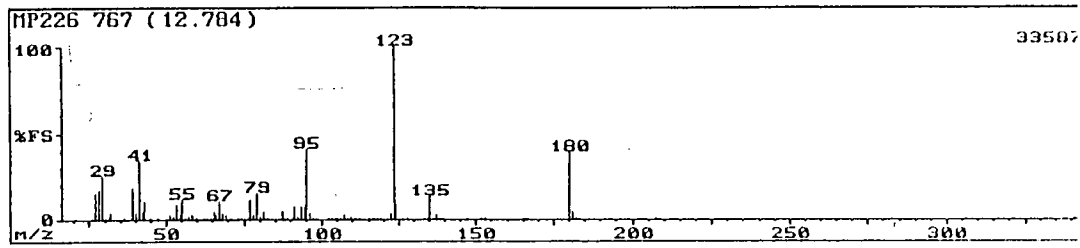
No. 18 1-Ethoxyadamantane (72)

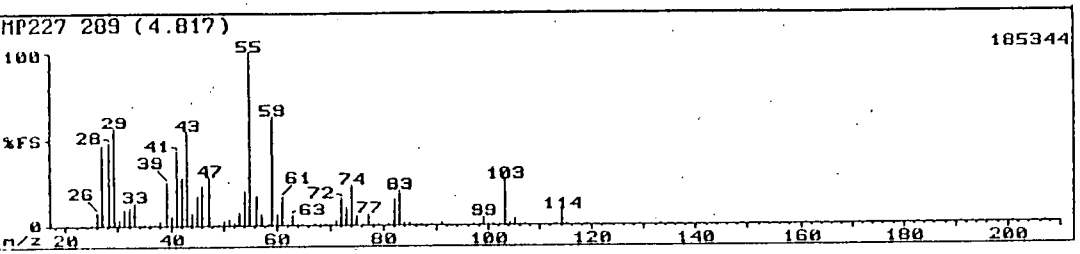
$M^{+\bullet} = 180$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.06	60	0.09	89	0.19	122	3.64
26	0.94	62	0.17	90	0.20	123	100.00
27	15.63	63	0.39	91	7.93	124	9.83
28	17.30	64	0.26	92	2.23	125	0.91
29	25.61	65	4.82	93	8.16	126	0.11
30	1.35	66	2.82	94	7.77	128	0.04
31	2.29	67	11.05	95	40.85	133	0.25
32	4.19	68	3.73	96	3.94	134	1.19
36	0.09	69	2.69	97	0.66	135	13.41
39	18.60	70	0.48	98	0.13	136	1.12
40	3.79	71	0.26	102	0.08	137	3.26
41	33.54	73	0.49	103	0.35	138	0.59
42	4.73	74	0.09	104	0.16	139	0.13
43	10.37	75	0.09	105	1.15	147	0.11
44	0.64	76	0.36	106	0.32	151	0.12
45	1.22	77	11.51	107	2.88	152	0.11
47	0.11	78	3.09	108	0.60	153	0.22
50	0.62	79	15.85	109	1.70	165	0.24
51	2.72	80	1.98	110	0.79	166	0.08
52	1.96	81	4.95	111	1.24	180	38.41
53	8.77	82	1.09	112	0.24	181	4.98
54	2.86	83	0.69	115	0.34	182	0.41
55	12.04	84	0.16	116	0.11	207	0.08
56	1.18	85	0.06	117	0.30	341	0.10
57	1.71	86	1.31	118	0.08		
58	3.18	87	4.57	119	0.18		
59	1.33	88	0.17	121	0.07		

No. 19 Methyl 3-fluorovalerate (74A) and Methyl 4-fluorovalerate (74B)

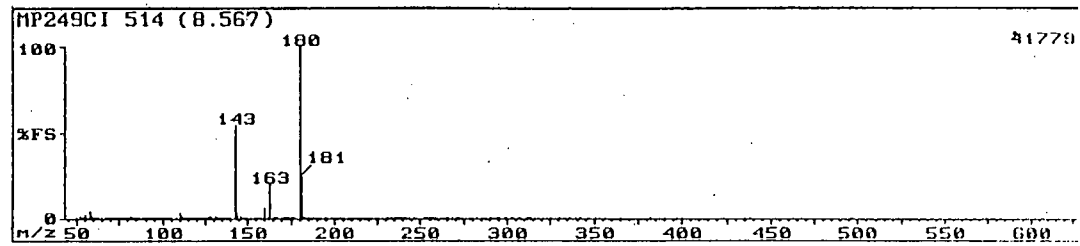
$M^{+\bullet} = 134$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.37	45	17.96	67	0.21	90	0.12
25	0.27	46	23.62	68	0.60	91	1.82
26	7.73	47	27.76	69	0.92	92	0.16
27	46.96	48	0.79	70	0.34	97	0.15
28	47.51	49	0.85	71	2.87	98	0.08
29	56.35	50	2.69	72	15.88	99	5.25
30	4.07	51	4.35	73	10.64	100	0.38
31	9.81	52	1.48	74	23.48	101	0.33
32	10.22	53	7.87	75	5.35	102	0.26
33	13.12	54	20.44	76	0.20	103	26.66
34	0.29	55	100.00	77	6.56	104	1.61
35	1.40	56	17.13	78	0.32	105	3.83
36	0.66	57	6.53	79	0.49	106	0.40
37	1.17	58	1.74	81	1.00	107	0.13
38	2.76	59	62.98	82	15.06	113	1.26
39	25.00	60	6.84	83	20.44	114	8.32
40	5.49	61	16.30	84	1.58	115	0.67
41	42.54	62	0.84	85	1.48	119	0.56
42	27.76	63	5.97	86	0.65	133	0.63
43	54.14	64	0.28	87	0.57	207	0.13
44	7.53	65	0.37	89	0.17		

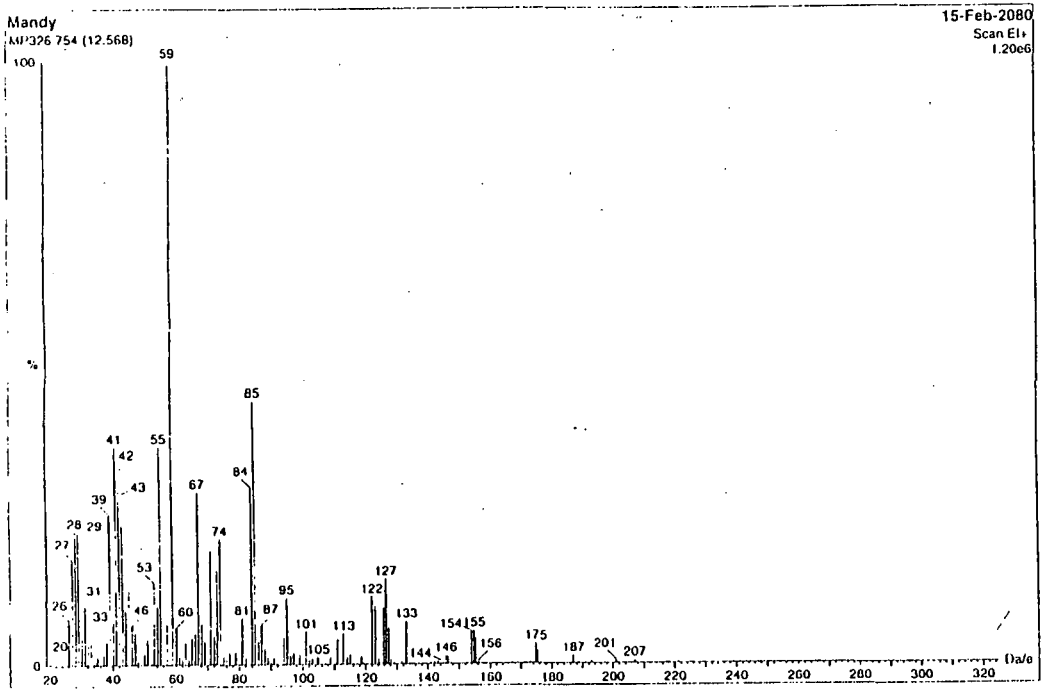
No. 20 Methyl 3-, 4-, 5-, and 6-fluoroenanthate (76A-D)

$M^{+\bullet} + NH_4^+ = 180$



No. 21 Dimethyl 3-fluoropimelate (79A) and Dimethyl 4-fluoropimelate (79B)

$M^{+\bullet} = 206$

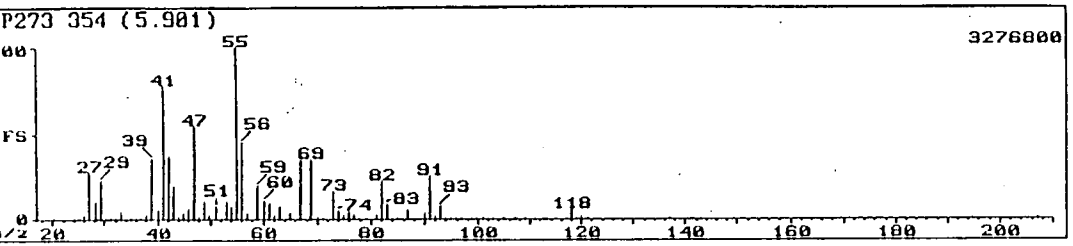


Mandy.
MP326 754 (12.568)
15-Feb-208
Scan EI

No	Mass	Inten	%BPI	%TIC	No	Mass	Inten	%BPI	%TIC	No	Mass	Inten	%BPI	%TIC	No	Mass	Inten	%BPI	%TIC
1:	20	5.57e3	0.47	0.06	42:	65	5.35e4	4.47	0.56	83:	116	3.49e3	0.29	0.04	124:	161	1.34e3	0.11	0.01
2:	21	1.30e2	0.01	0.00	43:	66	6.12e4	5.12	0.64	84:	117	1.09e3	0.09	0.01	125:	163	3.60e2	0.03	0.00
3:	24	4.22e3	0.35	0.04	44:	67	3.44e5	28.77	3.58	85:	119	1.52e4	1.27	0.16	126:	165	5.76e2	0.05	0.01
4:	26	8.60e4	7.19	0.89	45:	68	7.99e4	6.68	0.83	86:	119	4.67e3	0.39	0.05	127:	169	1.54e3	0.13	0.02
5:	27	2.08e5	17.38	2.16	46:	69	4.53e4	3.79	0.47	87:	120	1.50e3	0.13	0.02	128:	172	4.36e2	0.04	0.00
6:	28	2.66e5	22.26	2.77	47:	71	2.25e5	18.84	2.34	88:	122	1.33e5	11.13	1.38	129:	173	3.52e3	0.29	0.04
7:	29	2.62e5	21.92	2.73	48:	72	5.56e4	4.64	0.58	89:	123	1.14e5	9.50	1.18	130:	175	3.97e4	3.32	0.41
8:	30	5.32e4	4.45	0.55	49:	73	1.90e5	15.92	1.98	90:	124	1.06e4	0.89	0.11	131:	175	2.64e4	2.20	0.27
9:	31	1.15e5	9.59	1.19	50:	74	2.51e5	20.98	2.61	91:	126	1.11e5	9.25	1.15	132:	176	2.10e3	0.18	0.02
10:	32	4.20e4	3.51	0.44	51:	75	1.59e4	1.33	0.17	92:	127	1.69e5	14.13	1.76	133:	177	3.16e2	0.03	0.00
11:	33	6.35e4	5.31	0.66	52:	76	8.70e3	0.73	0.09	93:	127	7.17e4	5.99	0.75	134:	184	4.16e2	0.03	0.00
12:	34	3.70e3	0.32	0.04	53:	77	2.43e4	2.03	0.25	94:	128	1.06e4	0.89	0.11	135:	186	1.70e3	0.14	0.02
13:	35	1.59e4	1.33	0.17	54:	79	2.51e4	2.10	0.26	95:	129	3.95e3	0.33	0.04	136:	187	1.56e4	1.31	0.16
14:	36	1.74e4	1.46	0.18	55:	81	9.22e4	7.71	0.96	96:	130	9.96e2	0.08	0.01	137:	189	3.02e3	0.25	0.03
15:	37	1.92e4	1.61	0.20	56:	82	1.29e4	1.08	0.13	97:	132	4.86e3	0.41	0.05	138:	191	1.30e2	0.01	0.00
16:	38	4.51e4	3.77	0.47	57:	84	3.52e5	29.45	3.66	98:	133	8.40e4	7.02	0.87	139:	193	5.12e3	0.43	0.05
17:	39	2.99e5	25.00	3.11	58:	85	5.24e5	43.84	5.45	99:	134	4.42e3	0.37	0.05	140:	201	5.76e3	0.48	0.06
18:	40	8.29e4	6.93	0.86	59:	86	5.25e4	4.39	0.55	100:	135	8.20e2	0.07	0.01	141:	202	3.60e2	0.03	0.00
19:	41	4.34e5	36.30	4.52	60:	87	7.68e4	6.42	0.80	101:	136	2.92e2	0.02	0.00	142:	205	1.37e2	0.01	0.00
20:	42	3.85e5	32.19	4.00	61:	88	3.07e4	2.57	0.32	102:	137	9.08e2	0.08	0.01	143:	207	8.27e3	0.52	0.07
21:	43	3.40e5	28.42	3.54	62:	89	1.74e4	1.46	0.18	103:	139	1.78e3	0.15	0.02	144:	208	4.24e2	0.04	0.00
22:	44	1.08e5	8.99	1.12	63:	90	6.34e3	0.53	0.07	104:	139	1.65e3	0.14	0.02	145:	209	4.64e2	0.04	0.00
23:	45	1.44e5	12.07	1.50	64:	91	1.34e4	1.12	0.14	105:	141	3.49e3	0.29	0.04	146:	219	1.86e2	0.02	0.00
24:	46	7.58e4	6.34	0.79	65:	92	3.34e3	0.28	0.03	106:	142	4.00e3	0.33	0.04	147:	221	2.08e3	0.17	0.02
25:	47	6.22e4	5.20	0.65	66:	94	5.30e4	4.43	0.55	107:	143	4.99e3	0.42	0.05	148:	225	5.80e2	0.05	0.01
26:	48	9.09e3	0.76	0.09	67:	95	1.32e5	11.04	1.37	108:	144	5.63e3	0.47	0.06	149:	229	3.32e2	0.03	0.00
27:	49	6.66e3	0.56	0.07	68:	96	1.79e4	1.50	0.19	109:	145	2.02e3	0.17	0.02	150:	239	2.64e2	0.02	0.00
28:	50	2.20e4	1.84	0.23	69:	97	2.36e4	1.97	0.24	110:	146	1.66e4	1.39	0.17					
29:	51	4.86e4	4.07	0.51	70:	98	2.00e4	1.67	0.21	111:	146	1.47e4	1.23	0.15					
30:	52	9.09e3	0.76	0.09	71:	99	2.02e4	1.69	0.21	112:	147	1.81e3	0.15	0.02					
31:	53	1.62e5	13.53	1.68	72:	101	6.40e4	5.35	0.67	113:	148	5.20e2	0.04	0.01					
32:	54	1.16e5	9.67	1.20	73:	102	7.94e3	0.66	0.08	114:	149	3.16e2	0.03	0.00					
33:	55	4.34e5	36.30	4.52	74:	103	1.20e4	1.01	0.13	115:	152	5.20e2	0.04	0.01					
34:	56	4.45e4	3.72	0.46	75:	105	1.41e4	1.18	0.15	116:	153	2.11e3	0.18	0.02					
35:	57	7.99e4	6.68	0.83	76:	106	1.66e3	0.14	0.02	117:	154	6.30e4	5.27	0.66					
36:	59	1.20e6	100.00	12.44	77:	107	1.15e3	0.10	0.01	118:	155	6.50e4	5.44	0.68					
37:	60	7.17e4	5.99	0.75	78:	109	1.32e4	1.11	0.14	119:	155	5.22e4	4.37	0.54					
38:	61	1.49e4	1.25	0.16	79:	111	4.99e4	4.17	0.52	120:	156	5.89e3	0.49	0.06					
39:	62	9.15e3	0.77	0.10	80:	113	5.99e4	5.01	0.62	121:	157	1.09e3	0.09	0.01					
40:	63	4.38e4	3.66	0.46	81:	114	1.41e4	1.18	0.15	122:	159	6.84e2	0.06	0.01					
41:	64	1.04e4	0.87	0.11	82:	115	1.84e4	1.54	0.19	123:	159	4.40e2	0.04	0.00					

No. 22 1-Chloro-4-fluorohexane (84B) and 1-Chloro-5-fluorohexane (84C)

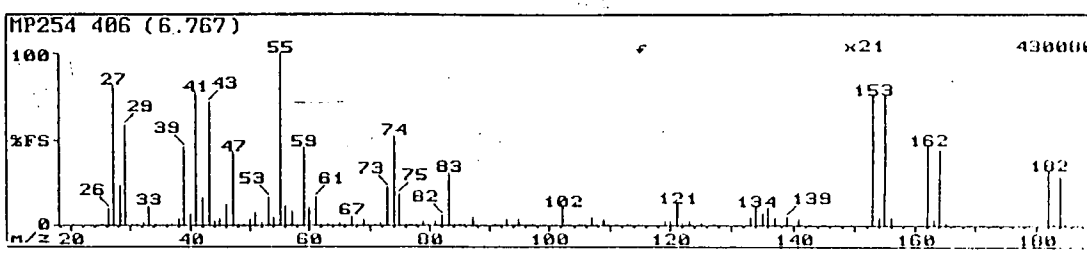
$M^{+\bullet} = 140$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.03	44	1.52	67	33.50	91	25.00
24	0.02	45	4.13	69	34.50	92	2.25
25	0.12	46	6.53	70	1.80	93	7.91
26	3.25	47	54.50	71	0.42	94	0.36
27	27.38	48	1.62	73	16.13	95	0.14
28	10.25	49	10.50	74	5.22	96	0.03
29	21.88	50	2.88	75	3.16	97	0.07
30	0.52	51	8.13	76	3.97	99	0.03
31	0.56	52	1.44	77	2.72	100	0.04
32	0.66	53	10.63	78	1.33	101	0.31
33	4.72	54	7.84	79	1.09	102	0.07
34	0.08	55	100.00	81	3.03	103	0.49
35	0.29	56	44.50	82	22.13	105	0.17
36	0.58	57	4.31	83	9.00	107	0.02
37	1.09	59	19.50	84	0.63	109	0.04
38	3.22	60	11.00	85	0.73	118	5.38
39	35.00	61	10.13	86	0.21	119	0.30
40	6.22	62	2.88	87	5.97	120	1.81
41	78.00	63	8.00	88	0.45	121	0.12
42	37.00	64	0.39	89	0.87	137	0.03
43	19.38	65	3.69	90	3.66	207	0.01

No. 23 1-Bromo-4-fluorohexane (82B) and 1-Bromo-5-fluorohexane (82C)

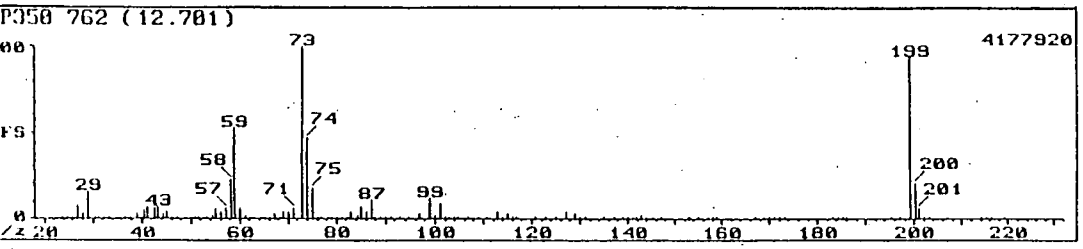
$M^{+\bullet} = 184$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.13	53	16.67	81	3.33	121	0.61
25	0.31	54	4.58	82	5.65	122	0.11
26	9.52	55	100.00	83	31.43	123	0.16
27	81.90	56	11.31	84	1.37	125	0.09
28	22.86	57	8.99	85	1.35	127	0.05
29	58.57	58	1.40	86	0.13	128	0.04
30	1.44	59	45.95	87	4.58	133	0.25
31	1.44	60	10.83	88	0.16	134	0.54
32	1.77	61	16.90	91	0.41	135	0.36
33	12.08	62	0.93	92	0.15	136	0.52
34	0.18	63	0.77	93	4.35	137	0.23
36	0.25	64	0.33	94	0.22	139	0.26
37	1.31	65	1.50	95	4.05	141	0.19
38	4.29	66	0.44	96	0.12	153	1.68
39	45.95	67	5.89	97	0.08	154	0.22
40	6.90	68	0.60	101	0.38	155	1.68
41	78.10	69	3.47	102	10.36	156	0.22
42	16.43	70	0.66	103	0.70	162	2.28
43	71.43	71	0.85	105	0.35	163	0.19
44	3.27	72	2.13	106	0.62	164	2.19
45	3.66	73	22.38	107	4.52	165	0.12
46	12.26	74	52.86	108	0.74	182	1.53
47	42.38	75	18.10	109	4.17	183	0.10
48	1.04	76	0.80	110	0.19	184	1.41
49	0.49	77	0.65	111	0.20	185	0.10
50	3.60	78	0.09	113	0.38		
51	8.21	79	2.69	119	0.14		
52	2.05	80	1.03	120	0.12		

No. 24 Decyltrimethylsilane (85)

$M^{+\bullet} = 216$

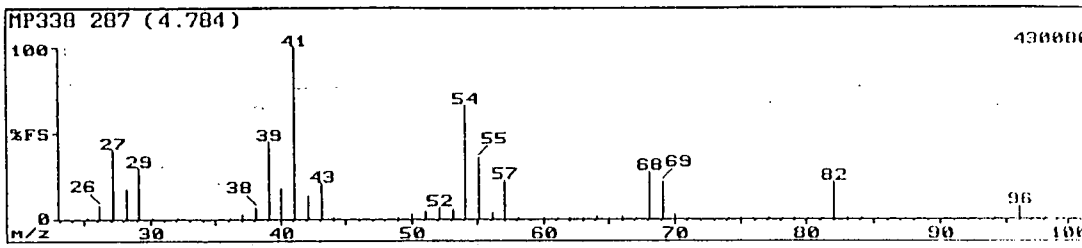


Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
24	0.01	58	22.25	91	0.09	143	1.52
25	0.02	59	52.55	93	0.17	144	0.13
26	0.24	60	5.91	95	0.72	145	0.05
27	7.55	61	2.35	97	2.77	147	0.02
28	2.75	62	0.11	99	11.76	153	0.02
29	15.10	63	0.08	100	1.86	153	0.01
31	0.97	64	0.10	101	8.63	155	0.22
31	0.99	65	0.39	102	0.88	157	0.65
32	0.11	66	0.71	103	0.32	158	0.09
33	0.03	67	2.50	104	0.04	159	0.02
36	0.01	68	1.42	105	0.03	167	0.03
36	0.03	69	4.17	107	0.03	169	0.34
38	0.04	70	3.85	109	0.25	170	0.03
39	3.01	71	6.20	111	0.51	171	0.77
40	0.22	73	100.00	113	4.31	172	0.12
41	4.75	74	46.27	114	0.45	173	0.02
41	6.76	75	17.94	115	2.72	183	0.06
43	5.96	76	0.73	116	0.30	184	0.02
43	6.86	77	0.49	117	0.13	185	0.01
44	2.72	78	0.13	121	0.02	186	0.03
45	3.50	79	0.50	123	0.06	195	0.02
46	0.30	80	0.30	125	0.13	197	0.53
47	0.12	81	1.16	127	4.07	199	94.51
50	0.05	82	1.00	129	3.09	200	20.78
51	0.15	83	3.87	130	0.33	201	5.44
52	0.03	84	1.84	131	0.12	202	0.57
52	0.46	85	6.96	135	0.03	203	0.07
53	1.10	86	3.55	137	0.36	214	0.22
54	2.35	87	10.39	139	1.33	215	0.08
55	5.61	88	1.01	140	0.76	216	0.02
56	3.58	89	0.37	141	1.34	219	0.02
57	6.08	90	0.03	142	0.11		

B15

No. 25 Hexanenitrile (87)

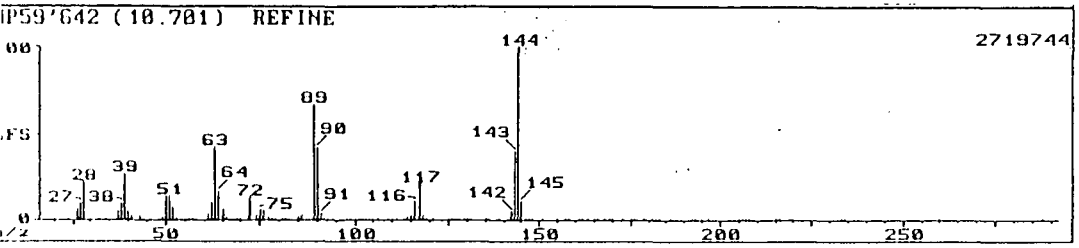
$M^{+\bullet} = 97$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
25	0.32	43	20.24	62	0.51	78	0.13
26	7.98	44	0.90	63	0.87	79	0.94
27	40.24	49	0.40	64	1.59	80	1.13
28	17.38	50	2.62	65	0.87	81	0.36
29	29.05	51	4.76	66	1.50	82	21.67
30	1.12	52	6.37	67	1.25	83	1.22
32	0.27	53	5.60	68	27.62	84	0.05
36	0.19	54	65.71	69	21.43	94	0.19
37	2.63	55	34.52	70	2.90	96	7.38
38	6.85	56	3.65	71	0.25	97	0.43
39	44.29	57	22.14	74	0.06	98	0.69
40	17.62	58	1.03	75	0.22	99	0.06
41	100.00	60	0.07	76	0.15		
42	13.75	61	0.35	77	0.12		

No. 26 6-Methylquinoxaline (88)

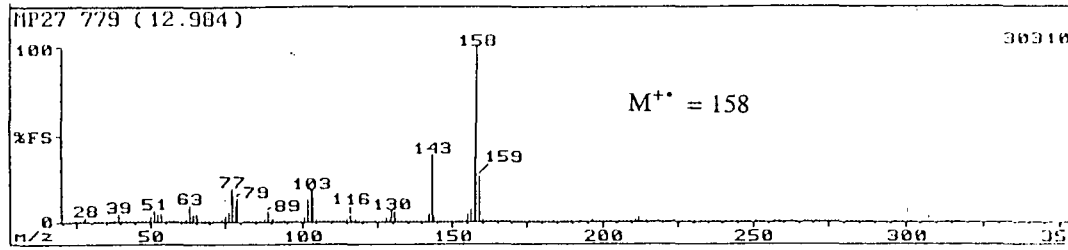
$M^{+\bullet} = 144$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.40	66	1.81	110	0.04	161	0.18
24	0.47	67	0.22	111	0.07	162	0.06
26	6.93	68	0.08	113	0.41	163	0.07
27	9.79	69	0.19	114	1.68	165	0.03
28	21.99	70	0.06	115	2.64	166	0.03
30	0.10	72	13.86	116	10.69	168	0.10
32	0.96	74	2.97	117	21.39	169	0.04
34	0.03	75	6.25	118	2.86	170	0.01
37	5.84	76	5.87	119	0.19	173	0.01
38	9.49	77	2.38	121	0.02	175	0.03
39	26.81	78	1.39	125	0.03	176	0.04
40	5.87	79	0.32	126	0.05	179	0.21
41	2.67	81	0.10	127	0.13	181	0.09
43	3.31	82	0.05	128	0.14	182	0.02
44	1.00	85	1.62	129	0.16	183	0.03
46	0.33	86	2.45	130	0.11	186	0.01
48	0.53	89	66.87	131	0.04	192	0.05
49	2.00	90	41.57	135	0.02	193	0.05
50	13.25	91	3.65	136	0.02	195	0.02
51	14.91	92	0.40	139	0.02	197	0.04
52	8.25	93	0.12	141	0.45	205	0.07
53	1.85	94	0.03	142	5.31	206	0.02
54	0.51	98	0.13	143	39.76	207	0.09
55	0.22	99	0.34	144	100.00	208	0.02
56	0.12	100	0.36	145	11.14	215	0.03
57	0.47	101	0.55	146	0.72	216	0.03
58	0.58	102	1.27	147	0.08	219	0.25
61	4.18	103	0.96	148	0.06	220	0.03
62	10.39	104	0.52	151	0.02	233	0.11
63	42.77	105	0.12	155	0.03	234	0.05
64	16.87	106	0.11	157	0.03	260	0.01
65	6.51	109	0.02	158	0.03	288	0.05

B16

No. 27 6,7-Dimethylquinoxaline (89)

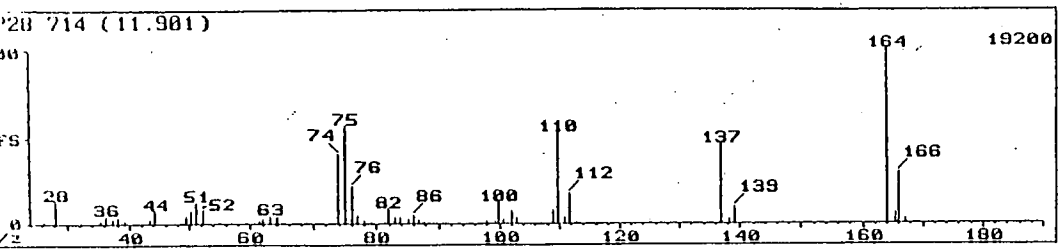


$M^{+\bullet} = 158$

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
24	0.02	81	0.27	135	0.07	189	0.06
25	0.04	82	0.12	136	0.04	190	0.23
26	0.63	83	0.12	137	0.07	191	0.85
27	0.99	84	0.09	138	0.09	192	0.60
28	3.14	85	0.29	139	0.10	193	0.38
29	0.10	86	0.65	140	0.23	194	0.42
31	0.07	87	1.33	141	0.53	195	0.26
33	0.05	88	2.03	142	4.46	196	0.44
33	0.03	89	5.57	143	38.38	197	2.33
35	0.03	90	2.36	144	4.09	198	0.28
36	0.10	91	1.72	145	0.43	199	0.11
37	0.64	92	0.57	146	0.16	200	0.04
38	1.43	93	0.27	147	0.14	201	0.02
39	5.34	94	0.23	148	0.07	202	0.02
40	0.82	95	0.20	149	0.05	203	0.05
41	1.06	96	0.17	150	0.12	204	0.07
42	0.21	97	0.11	151	0.18	205	0.19
43	0.13	98	0.50	152	0.21	206	0.42
44	0.22	99	0.68	153	0.24	207	0.21
45	0.06	100	0.74	154	0.68	208	0.23
46	0.03	101	3.07	155	5.10	209	0.60
47	0.03	102	13.11	156	7.74	210	0.48
48	0.24	103	18.92	157	37.30	211	1.56
49	0.70	104	18.92	158	100.00	212	2.87
50	3.61	105	2.03	159	26.22	213	0.65
51	6.59	106	0.29	160	2.36	214	0.09
52	4.86	107	0.28	161	0.41	215	0.12
53	5.14	108	0.12	162	0.09	216	0.05
54	1.33	109	0.04	163	0.17	217	0.07
55	0.15	110	0.03	164	0.19	218	0.06
56	0.08	111	0.05	165	0.21	219	0.22
57	0.24	112	0.15	166	0.21	220	0.23
58	0.15	113	0.19	167	0.07	221	0.34
59	0.07	114	1.23	168	0.12	222	0.05
60	0.12	115	1.77	169	0.15	223	0.11
61	0.85	116	3.68	170	0.20	224	0.05
62	2.33	117	1.42	171	0.26	225	0.02
63	9.86	118	1.47	172	0.14	226	0.02
64	4.59	119	0.45	173	0.22	227	0.02
65	4.66	120	0.24	174	0.09	228	0.03
66	1.71	121	0.10	175	0.07	229	0.13
67	0.38	122	0.04	176	0.29	230	0.26
68	0.15	123	0.04	177	0.22	231	0.10
69	0.18	124	0.11	178	0.16	232	0.06
70	0.14	125	0.22	179	0.61	233	0.20
71	0.11	126	0.29	180	0.11	234	0.25
72	0.10	127	0.70	181	0.20	235	0.75
73	0.45	128	2.94	182	0.46	236	0.18
74	2.07	129	1.88	183	0.18	237	0.04
75	3.55	130	6.76	184	0.12	238	0.01
76	5.51	131	5.78	185	0.17	239	0.02
77	19.59	132	1.01	186	0.04	240	0.01
78	9.86	133	0.09	187	0.04	241	0.02
79	11.78	134	0.10	188	0.02	242	0.02

No. 28 6-Chloroquinoxaline (90)

$M^{+\bullet} = 166$

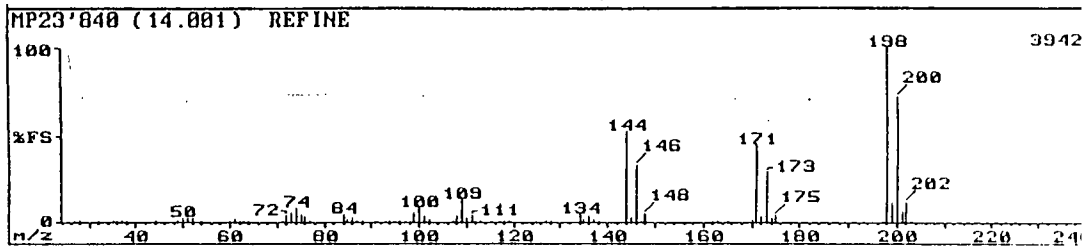


Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
26	2.15	52	8.25	79	1.33	103	3.88
28	13.50	55	1.14	81	1.11	109	7.58
32	1.17	59	0.64	82	8.83	110	52.67
35	2.27	61	1.81	83	4.10	111	4.25
36	5.29	62	2.94	84	3.42	112	17.00
37	3.06	63	5.25	85	2.46	113	1.44
38	3.94	64	1.92	86	4.40	137	45.67
39	2.00	65	0.97	87	2.46	138	2.52
43	3.40	69	0.71	88	1.29	139	9.75
44	8.00	74	39.33	98	1.75	164	100.00
49	1.04	75	56.60	99	1.46	165	6.58
49	4.67	76	21.00	100	12.92	166	28.67
50	8.25	77	4.67	101	3.31	167	2.46
51	12.42	78	2.78	102	7.92		

B17

No. 29 6,7-Dichloroquinoxaline (91)

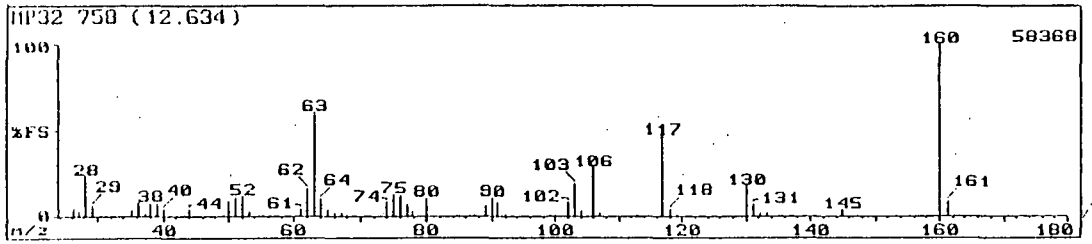
$M^{+\bullet} = 202$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
27	0.44	72	3.81	107	0.34	147	0.87
28	0.93	73	5.48	108	3.61	148	4.95
32	0.62	74	8.32	109	13.31	162	0.50
35	0.52	75	5.07	110	3.25	163	1.13
36	1.02	76	4.26	111	3.45	165	0.57
37	1.45	77	0.88	112	0.65	170	2.11
38	0.86	84	4.67	113	0.82	171	44.81
44	0.38	85	2.09	118	0.97	172	3.81
49	0.83	86	3.37	119	0.65	173	28.73
50	3.37	87	1.14	127	1.30	174	2.50
51	1.91	88	1.08	128	0.92	175	3.94
52	2.09	94	0.53	134	4.71	197	1.20
54	0.96	96	0.88	135	1.55	198	100.00
60	0.94	97	0.81	136	3.53	199	11.69
61	1.46	98	1.29	137	1.82	200	71.43
62	1.30	99	5.52	138	1.22	201	6.86
63	0.59	100	9.13	144	51.95	202	11.53
64	0.70	101	3.53	145	3.17	203	0.91
71	0.51	102	1.58	146	33.12		

No. 30 6-Methoxyquinoxaline (92)

$M^{+\bullet} = 160$

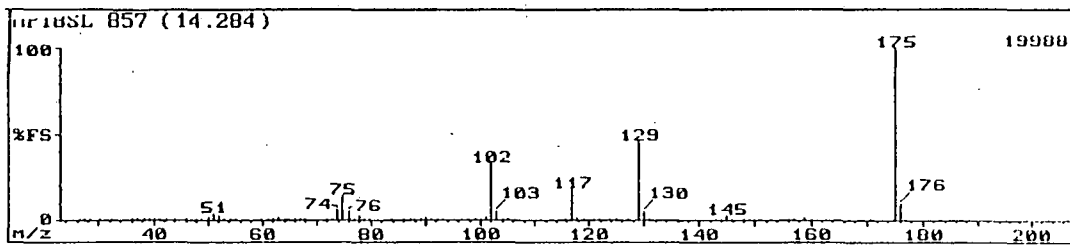


Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
26	4.39	44	3.48	74	7.35	106	27.74
27	3.34	49	0.86	75	12.94	107	1.86
28	23.25	50	8.88	76	11.29	117	46.93
29	5.70	51	10.75	77	6.58	118	4.00
30	1.01	52	11.51	78	3.34	119	0.38
31	1.03	53	2.85	80	10.53	130	17.54
32	0.56	55	1.05	87	0.40	131	7.24
35	3.89	56	0.88	89	5.95	132	1.69
36	7.46	61	4.22	90	11.07	133	1.73
37	3.28	62	15.46	91	7.46	145	4.00
38	7.68	63	60.53	92	1.02	160	100.00
39	7.13	64	9.65	99	0.58	161	8.33
40	4.19	65	3.76	100	0.51	162	0.62
41	1.14	66	1.75	102	7.35		
42	0.99	67	2.17	103	18.75		
43	1.00	68	1.09	104	3.34		

B18

No. 31 6-Nitroquinoxaline (93)

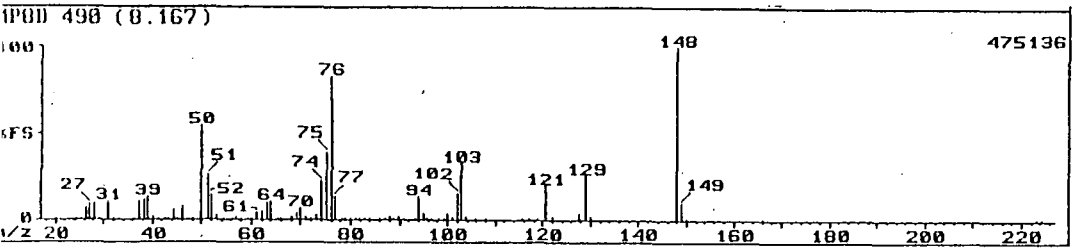
$M^{+\bullet} = 175$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
26	0.11	60	0.07	89	0.21	129	45.90
27	0.06	61	0.63	90	1.82	130	4.41
28	0.30	62	1.10	91	0.85	131	0.24
30	0.51	63	1.90	92	0.06	143	0.08
32	0.03	64	1.40	93	0.02	144	0.03
36	0.04	65	0.45	98	0.05	145	3.38
37	0.27	66	0.17	99	0.66	146	0.32
38	0.34	67	0.08	100	1.11	148	0.86
39	0.24	68	0.06	101	2.19	149	0.21
40	0.12	72	0.04	102	33.40	150	0.02
41	0.03	73	1.00	103	4.61	156	0.03
42	0.02	74	6.30	104	0.21	157	0.03
44	0.02	75	14.96	105	0.05	159	1.54
46	0.40	76	4.41	116	0.13	160	0.14
48	0.05	77	0.85	117	18.85	171	0.03
49	0.30	78	3.20	118	1.69	175	100.00
50	2.20	79	0.60	119	0.06	176	9.94
51	4.25	80	0.04	121	0.12	177	0.95
52	2.91	84	0.04	122	0.02	207	0.02
53	0.24	86	0.15	124	0.02		
54	0.04	87	0.20	125	0.02		
55	0.01	88	0.48	127	0.20		

No. 32 2-Fluoroquinoxaline (95)

$M^{+\bullet} = 148$

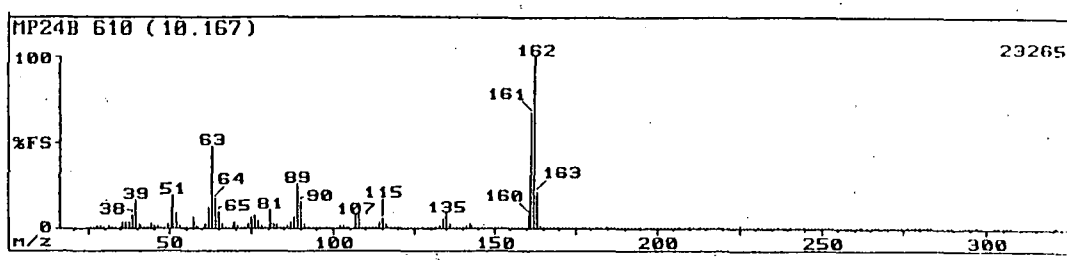


Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.10	51	26.08	76	83.62	101	2.02
24	0.23	52	14.87	77	14.01	102	15.95
25	1.14	53	2.56	78	1.28	103	33.41
26	7.22	54	0.10	79	0.46	104	2.14
27	8.94	56	0.81	80	0.15	106	0.13
28	9.81	57	2.24	81	1.16	108	0.22
29	0.36	58	1.12	82	0.69	116	0.25
31	10.61	59	0.10	83	0.43	117	0.09
32	0.45	60	0.72	84	0.19	119	0.48
33	0.26	61	3.56	86	0.65	121	20.47
36	1.10	62	5.12	87	1.24	122	1.90
37	10.51	63	9.54	88	1.75	128	4.04
38	11.64	64	11.15	89	1.09	129	25.86
39	13.25	65	0.98	90	1.97	130	2.32
40	1.79	66	0.48	91	0.42	148	100.00
41	0.81	68	2.34	93	0.96	149	9.70
42	0.14	69	3.50	94	13.15	150	0.53
43	0.70	70	6.90	95	3.42	166	0.12
44	6.25	71	1.54	96	1.40	223	0.36
45	1.27	72	0.49	97	1.31	224	0.10
46	7.92	73	2.99	98	0.18		
48	0.69	74	22.20	99	0.73		
50	54.09	75	39.01	100	4.36		

B19

No. 33 2-Fluoro-6-methylquinoxaline (96A) and 2-Fluoro-7-methquinoxaline (96B)

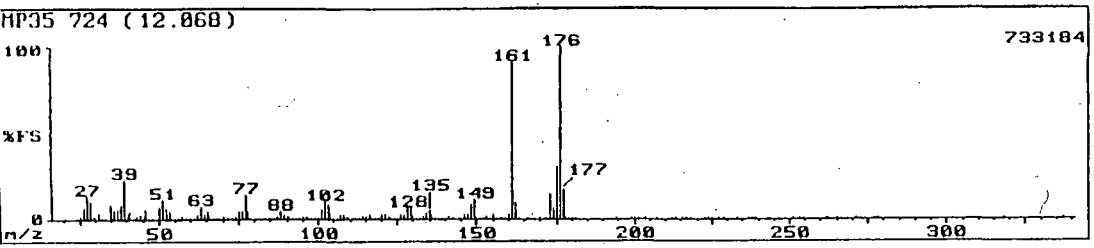
$M^{+\bullet} = 162$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.01	78	2.05	132	1.41	186	0.72
24	0.09	79	0.34	133	2.19	187	0.21
25	0.27	80	1.43	134	6.03	188	0.05
26	1.41	81	10.83	135	8.93	189	0.11
27	1.77	82	2.53	136	2.46	190	0.03
28	2.35	83	2.95	137	0.22	191	0.04
29	0.07	84	1.32	138	0.05	192	0.04
31	1.97	85	1.06	139	0.08	193	0.13
32	0.20	86	1.75	140	0.72	194	0.01
33	0.31	87	3.48	141	1.90	195	0.08
35	0.75	88	6.69	142	2.86	196	0.09
35	3.57	89	26.41	143	2.11	197	0.51
36	3.92	90	15.49	144	0.27	198	0.69
37	3.70	91	2.61	145	0.13	199	0.55
38	7.48	92	0.45	146	0.16	200	0.37
39	16.90	93	0.81	147	0.33	201	1.09
40	3.13	94	1.24	148	0.37	202	0.18
41	1.54	95	1.02	149	0.12	203	0.10
42	0.34	96	0.90	150	0.07	204	0.15
43	0.92	97	0.81	151	0.12	205	0.07
44	2.54	98	0.19	152	0.18	206	0.03
45	2.18	99	0.50	153	0.13	207	0.04
46	1.86	100	1.09	154	0.08	208	0.03
47	0.21	101	0.68	155	0.04	209	0.11
48	0.86	102	1.51	156	0.02	210	0.50
49	2.62	103	1.46	157	0.04	211	0.30
50	11.62	104	0.59	158	0.07	212	0.07
51	19.01	105	0.41	159	0.88	213	0.35
52	9.20	106	1.42	160	7.44	214	0.05
53	2.39	107	8.01	161	66.90	215	0.06
54	0.73	108	7.66	162	100.00	216	0.09
55	0.21	109	1.39	163	21.48	217	0.11
56	1.39	110	0.38	164	1.71	218	0.12
57	6.65	111	0.35	165	0.17	219	0.42
58	2.24	112	0.21	166	0.16	220	0.10
59	1.05	113	0.74	167	0.12	221	0.03
60	0.86	114	4.36	168	0.05	222	0.15
61	3.35	115	5.55	169	0.05	223	0.56
62	13.03	116	3.13	170	0.09	224	0.73
63	47.18	117	1.07	171	0.08	225	1.86
64	17.25	118	0.18	172	0.09	226	0.42
65	9.29	119	0.24	173	0.15	227	0.15
66	2.79	120	0.36	174	0.06	228	0.12
67	1.11	121	0.69	175	0.12	229	0.09
68	1.19	122	0.18	176	0.06	230	0.02
69	1.95	123	0.21	177	0.10	231	0.05
70	3.43	124	0.04	178	0.12	232	0.05
71	1.54	125	0.30	179	0.45	233	0.01
72	0.42	126	0.24	180	0.46	235	0.13
73	0.69	127	0.24	181	0.13	235	0.06
74	2.62	128	0.13	182	0.04	236	0.12

No. 34 2-Fluoro-6,7-dimethylquinoxaline (97)

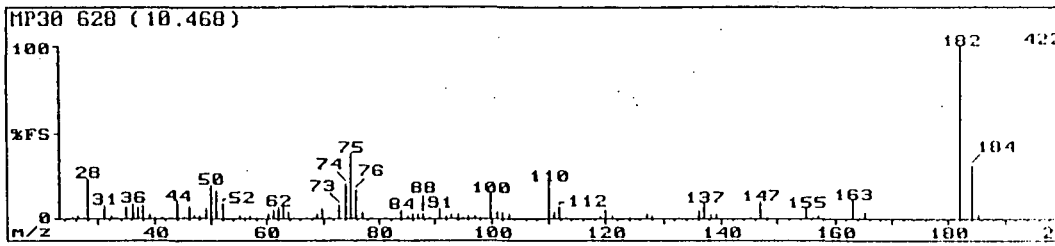
$M^{+\bullet} = 176$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.19	70	1.64	116	2.93	162	9.64
24	0.79	71	0.84	117	0.82	163	0.59
25	1.47	72	0.36	118	0.33	166	0.05
26	6.77	73	0.41	119	0.84	170	0.08
27	13.97	74	2.09	120	2.62	171	0.09
28	11.03	75	4.43	121	2.93	172	0.47
29	1.93	76	4.50	122	1.99	173	14.66
30	0.26	77	14.53	123	0.73	174	6.77
31	3.95	78	4.57	124	0.17	175	31.15
32	0.45	79	0.75	125	0.14	176	100.00
33	0.56	80	0.24	126	2.44	177	17.32
35	8.94	81	1.10	127	3.21	178	1.38
36	5.66	82	0.87	128	7.02	179	0.14
37	6.18	83	1.29	129	6.39	180	0.07
38	8.31	84	0.69	130	2.18	181	0.03
39	23.74	85	0.55	131	0.54	194	0.05
40	2.90	86	0.55	132	1.38	199	0.09
41	5.31	87	1.87	133	2.30	200	0.27
42	0.96	88	4.47	134	4.29	201	0.07
43	1.73	89	3.39	135	5.10	203	0.07
44	2.93	90	1.76	136	2.55	207	0.06
45	0.93	91	1.61	137	0.49	212	0.08
46	5.41	92	0.38	138	0.07	213	0.05
47	0.28	93	0.29	139	0.14	215	0.23
48	0.54	94	0.73	140	0.85	216	0.05
49	1.20	95	2.21	141	1.71	217	0.08
50	8.24	96	1.64	142	0.88	218	0.06
51	11.17	97	1.32	143	0.26	223	0.07
52	6.95	98	0.69	144	0.06	224	0.12
53	4.47	99	0.96	145	0.57	225	0.07
54	0.97	100	1.16	146	3.00	227	0.14
55	0.66	101	5.97	147	2.44	229	0.04
56	0.59	102	10.20	148	8.83	233	0.10
57	2.34	103	8.34	149	11.17	237	0.08
58	0.90	104	3.91	150	1.30	238	0.07
59	0.38	105	0.86	151	0.15	239	0.13
60	0.29	106	0.65	152	0.14	251	0.10
61	1.13	107	2.76	153	2.16	253	0.46
62	2.65	108	2.90	154	0.42	254	0.12
63	8.17	109	1.47	155	3.21	262	0.05
64	4.19	110	0.51	156	0.58	265	0.04
65	4.47	111	0.45	157	1.42	271	0.03
66	1.41	112	0.27	158	0.27	277	0.11
67	0.51	113	0.47	159	0.83	278	0.10
68	0.29	114	1.94	160	3.35	337	0.11
69	0.66	115	1.67	161	91.62		

No. 35 6-Chloro-2-fluoroquinoxaline (98A) and 7-Chloro-2-fluoroquinoxaline (98B)

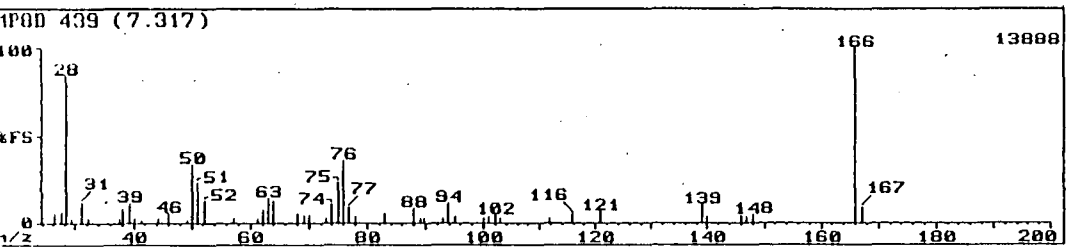
$M^{+\bullet} = 184$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
25	0.73	55	1.72	88	3.03	127	2.99
26	2.42	56	1.43	89	0.68	128	1.53
28	1.01	57	1.72	91	6.21	136	4.51
28	23.48	58	1.36	92	2.38	137	9.20
31	8.11	60	2.65	93	2.92	138	2.50
32	2.26	61	4.70	94	2.46	139	2.92
35	6.70	62	7.27	95	1.31	145	0.64
36	8.94	63	7.23	96	1.70	147	9.36
37	7.12	64	3.41	97	1.80	148	0.98
38	7.58	68	1.18	98	1.01	155	6.17
39	2.54	69	2.92	100	14.85	156	0.72
40	0.80	70	5.68	101	3.90	157	1.94
41	0.61	71	0.93	102	3.41	163	11.06
44	9.85	73	8.03	103	2.46	164	1.43
45	1.22	74	20.30	110	21.82	165	3.60
46	7.01	75	38.33	111	3.64	182	100.00
47	1.97	76	16.67	112	6.97	184	31.36
48	1.46	77	3.41	113	0.76	185	2.46
49	5.72	84	5.15	119	2.00	200	1.76
50	19.39	85	1.97	120	4.66		
51	16.67	86	3.26	121	1.95		
52	8.33	87	2.58	124	1.27		

No. 36 2,3-Difluoroquinoxaline (100)

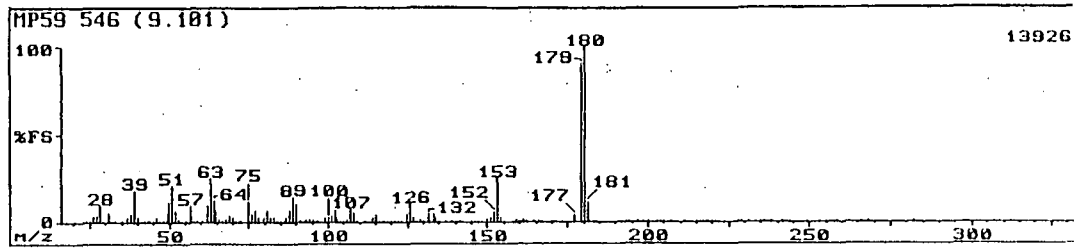
$M^{+\bullet} = 166$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
26	6.22	49	2.42	74	10.25	101	3.74
28	6.60	50	34.10	75	23.27	102	5.07
28	84.79	51	23.04	76	35.94	103	2.85
29	2.94	52	12.21	77	8.53	112	2.56
31	11.87	57	3.00	78	3.57	116	5.21
32	3.05	61	2.48	83	6.28	121	6.65
37	2.51	62	7.95	88	9.10	139	10.71
38	8.53	63	14.29	89	2.94	140	3.54
39	11.52	64	12.33	90	3.31	146	3.97
40	3.28	68	5.44	93	3.34	147	4.32
41	2.36	69	4.38	94	12.10	148	4.93
44	2.94	70	4.90	95	3.86	166	100.00
46	5.53	73	2.48	100	3.31	167	8.76

No. 37 2,3-Difluoro-6-methylquinoxaline (101)

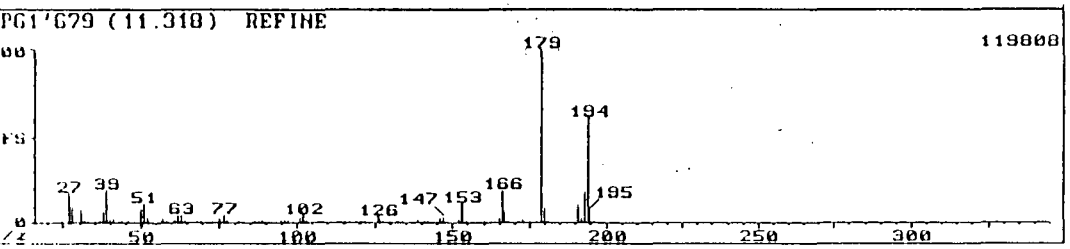
$M^{+\bullet} = 180$



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.24	73	0.50	122	0.16	191	0.10
24	0.68	75	11.91	123	0.19	192	0.04
25	1.19	76	5.07	125	4.56	193	0.10
26	3.71	77	6.69	126	10.22	194	0.06
27	3.95	78	2.70	127	2.48	197	0.15
28	9.49	80	3.25	128	1.34	198	0.09
29	0.62	81	6.54	129	2.37	200	0.01
31	5.96	82	2.76	130	0.30	203	0.06
32	1.43	83	2.83	132	5.22	204	0.15
33	0.27	84	0.66	133	5.07	205	0.05
35	0.04	85	0.60	134	2.79	207	0.06
37	2.48	86	1.02	135	0.66	211	0.13
38	4.65	87	3.22	137	0.43	215	0.04
39	18.24	88	6.62	138	0.75	216	0.09
40	2.57	89	14.49	139	1.01	217	0.16
41	1.36	90	11.10	140	0.62	218	0.06
42	0.53	91	1.23	141	0.71	219	0.40
43	1.21	92	0.08	142	0.18	220	0.05
44	1.34	92	1.03	145	0.28	221	0.02
45	1.01	93	2.00	146	0.18	222	0.02
46	2.98	94	2.21	147	0.47	227	0.03
47	0.38	95	1.53	148	0.14	228	0.02
48	1.07	96	0.46	150	1.89	229	0.04
49	1.58	97	0.11	151	3.16	231	0.06
50	11.40	99	2.52	152	5.88	235	0.03
51	20.88	100	3.13	153	25.00	236	0.03
52	6.32	101	3.44	154	2.79	237	0.12
53	2.17	102	6.91	155	0.17	238	0.02
54	0.63	103	2.90	158	1.34	241	0.09
55	0.14	104	0.57	159	1.88	242	0.08
56	1.34	105	0.69	160	1.31	243	0.17
57	9.49	106	1.73	161	1.65	244	0.04
58	0.76	107	7.57	162	0.14	249	0.02
59	0.70	108	5.88	164	0.30	253	0.03
61	1.15	109	0.78	165	0.32	255	0.05
62	9.26	111	0.33	166	0.20	256	0.03
63	25.00	112	0.92	167	0.07	257	0.03
64	12.87	113	1.25	170	0.01	258	0.02
65	6.99	114	3.29	171	0.03	261	0.04
66	2.10	115	4.52	177	3.84	262	0.04
67	0.61	116	1.18	179	90.59	266	0.03
68	1.88	117	0.16	180	100.00	268	0.03
69	3.62	118	0.50	181	11.69	280	0.02
70	2.90	119	0.47	182	0.73	282	0.05
71	0.38	120	0.38	183	0.04	333	0.09
72	0.14	121	0.45	184	0.13		

No. 38 2,3-Difluoro-6,7-dimethylquinoxaline (102)

$M^{+\bullet}$ = 194

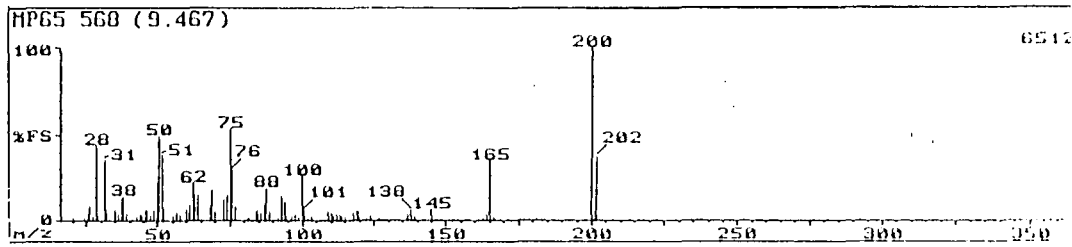


Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.18	59	0.18	101	3.07	148	1.04
24	0.44	61	2.35	102	5.02	152	1.98
25	0.66	62	4.27	103	2.03	153	11.38
27	17.09	63	4.49	104	0.51	154	1.24
28	10.47	64	1.91	107	0.81	155	0.24
29	1.11	65	0.80	108	0.74	158	0.28
31	7.85	66	0.52	113	0.25	159	0.75
32	1.62	68	0.30	114	1.26	160	0.62
33	0.47	69	0.51	115	0.80	161	0.35
35	0.33	70	0.74	116	1.06	165	2.44
36	0.97	73	0.93	117	0.46	166	7.64
37	2.11	74	1.16	119	0.69	167	7.00
38	6.36	75	2.84	120	1.44	168	0.69
39	19.66	76	2.10	121	1.11	171	1.36
40	2.98	77	4.91	122	0.38	173	1.79
41	2.55	78	1.74	126	3.63	175	0.66
43	1.01	81	0.81	127	1.63	177	0.81
44	1.87	82	0.52	128	1.22	179	100.00
45	0.84	83	0.48	129	1.16	180	9.03
46	1.79	86	0.44	130	0.36	181	0.37
48	0.39	87	0.50	132	0.84	190	0.72
49	1.38	88	1.08	133	0.69	191	10.36
50	8.39	89	1.90	134	0.70	192	2.96
51	11.43	90	0.66	139	1.70	193	18.59
52	4.17	91	0.51	140	0.78	194	61.54
53	2.31	95	2.27	141	0.89	195	6.52
54	0.20	96	1.48	142	0.59	196	0.29
56	0.93	97	1.51	145	0.95	341	0.45
57	2.75	99	1.19	146	2.63		
58	0.35	100	0.76	147	3.11		

B22

No. 39 2,3-Difluoro-6-chloroquinoxaline (103)

$M^{+\bullet}$ = 202



Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	1.51	70	5.86	117	0.30	163	1.76
24	1.89	71	0.70	118	5.03	164	4.01
25	3.89	73	12.58	119	5.54	165	34.75
26	9.20	74	15.88	120	5.39	166	2.67
27	3.38	75	53.46	121	0.60	167	0.10
28	44.03	76	29.56	122	0.79	169	1.00
29	2.51	77	8.96	123	0.39	171	0.40
30	0.66	80	1.28	124	3.30	172	0.10
31	35.22	81	2.19	125	0.95	173	1.31
32	6.37	82	2.11	126	1.20	174	0.19
33	0.26	83	0.40	127	1.66	175	0.39
35	6.88	84	6.25	128	0.86	176	0.07
36	3.69	85	6.45	129	0.78	177	0.05
37	13.36	86	4.56	130	0.41	179	0.09
38	14.31	87	9.47	131	0.18	180	0.19
39	4.64	88	19.81	132	0.05	181	1.50
40	1.15	89	6.09	133	0.51	182	0.21
41	0.12	90	1.05	134	0.78	183	0.49
42	0.95	91	0.99	135	0.46	184	0.40
43	2.67	92	1.54	136	1.89	191	0.12
44	4.05	93	14.78	137	4.32	200	100.00
44	4.25	94	11.32	138	6.21	201	5.62
46	6.37	95	2.83	139	2.99	202	37.26
46	6.64	96	0.59	140	0.49	207	0.30
47	3.46	97	2.83	141	0.05	213	0.08
49	6.41	98	3.50	142	0.18	216	0.07
50	23.43	99	3.26	143	0.05	218	0.12
50	49.06	100	26.57	144	0.21	229	0.07
51	37.89	101	5.82	145	6.72	231	0.26
52	7.98	102	2.11	146	0.86	234	0.14
53	0.85	103	3.18	147	0.16	236	0.06
55	2.52	104	1.22	148	0.12	237	0.07
56	5.03	105	0.62	149	0.65	238	0.03
57	4.17	106	0.94	150	0.49	262	0.03
58	0.57	107	0.73	151	0.24	275	0.06
60	6.60	108	0.71	152	0.26	276	0.06
61	9.51	109	5.66	153	0.15	281	0.05
62	22.64	110	4.80	154	0.33	292	0.07
63	15.09	111	3.93	155	1.03	329	0.09
64	15.57	112	3.46	156	0.21	365	0.14
65	1.03	113	4.17	157	0.39	367	0.04
66	0.74	114	3.26	158	0.03		
68	8.65	115	3.14	161	0.03		
69	18.24	116	0.33	162	0.13		

Appendix 3: IR Spectra

No. 1	Fluorocyclohexane (**37**)
No. 2	*cis*-9-Fluorodecalin (**47**)
No. 3	*trans*-9-Fluorodecalin (**49**)
No. 4	*trans*-1- and 2-Fluorodecalin (**63A-D**)
No. 5	*cis*-1- and 2-Fluorodecalin (**64A-D**)
No. 6	*exo*- and *endo*-2-Fluoronorbornane (**43A, B**)
No. 7	1-Fluoroadamantane (**44**)
No. 8	1-Fluoro-2-methylheptane (**51A**) and 1-Fluoro-6-methylheptane (**51B**)
No. 9	2-, 3-, 4-, and 5-Fluorodecane (**53A-D**)
No. 10	3β-Acetoxy-5α-androstanone (**55**)
No. 11	N-(1-Adamantyl)acetamide (**65**)
No. 12	N-(1-Adamantyl)propylamide (**66**)
No. 13	N-(Cyclohexyl)acetamide (**67**)
No. 14	N-(*trans*-9-Decalyl)acetamide (**68**)
No. 15	N-(*exo*-2-Norbornyl)acetamide (**69**)
No. 16	1-Aminoadamantane (**70**)
No. 17	1-Hydroxyadamantane (**71**)
No. 18	1-Ethoxyadamantane (**72**)
No. 19	Methyl 3-fluorovalerate (**74A**) and Methyl 4-fluorovalerate (**74B**)
No. 20	Methyl 3-, 4-, 5-, and 6-fluoroenanthate (**76A-D**)
No. 21	Dimethyl 3-fluoropimelate (**79A**) and Dimethyl 4-fluoropimelate (**79B**)
No. 22	1-Chloro-4-fluorohexane (**84B**) and 1-Chloro-5-fluorohexane (**84C**)
No. 23	1-Bromo-4-fluorohexane (**82B**) and 1-Bromo-5-fluorohexane (**82C**)
No. 24	Decyltrimethylsilane (**85**)
No. 25	Hexanenitrile (**87**)
No. 26	6-Methylquinoxaline (**88**)
No. 27	6,7-Dimethylquinoxaline (**89**)
No. 28	6-Chloroquinoxaline (**90**)
No. 29	6,7-Dichloroquinoxaline (**91**)
No. 30	6-Methoxyquinoxaline (**92**)
No. 31	6-Nitroquinoxaline (**93**)
No. 32	2-Fluoroquinoxaline (**95**)
No. 33	2-Fluoro-6-methylquinoxaline (**96A**) and 2-Fluoro-7-methylquinoxaline (**96B**)
No. 34	2-Fluoro-6,7-dimethylquinoxaline (**97**)

No. 35 6-Chloro-2-fluoroquinoxaline (**98A**) and
7-Chloro-2-fluoroquinoxaline (**98B**)

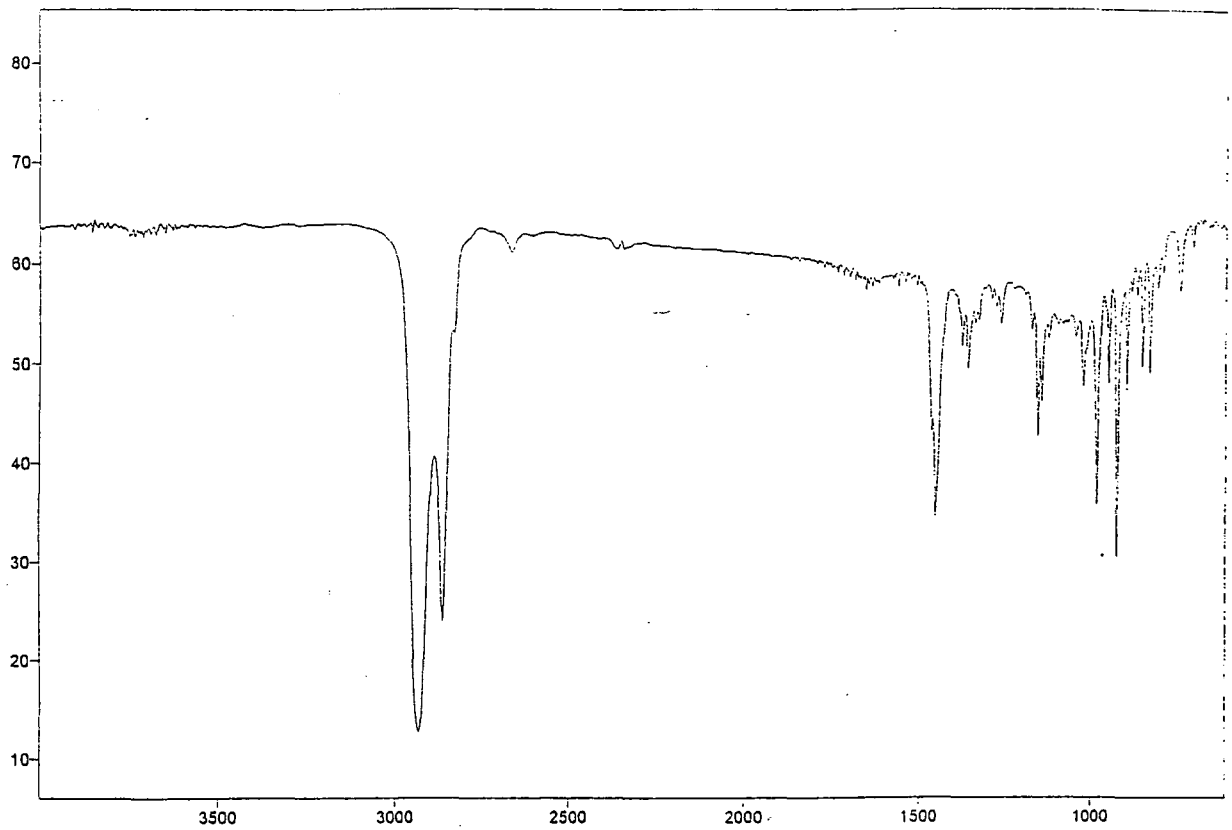
No. 36 2,3-Difluoroquinoxaline (**100**)

No. 37 2,3-Difluoro-6-methylquinoxaline (**101**)

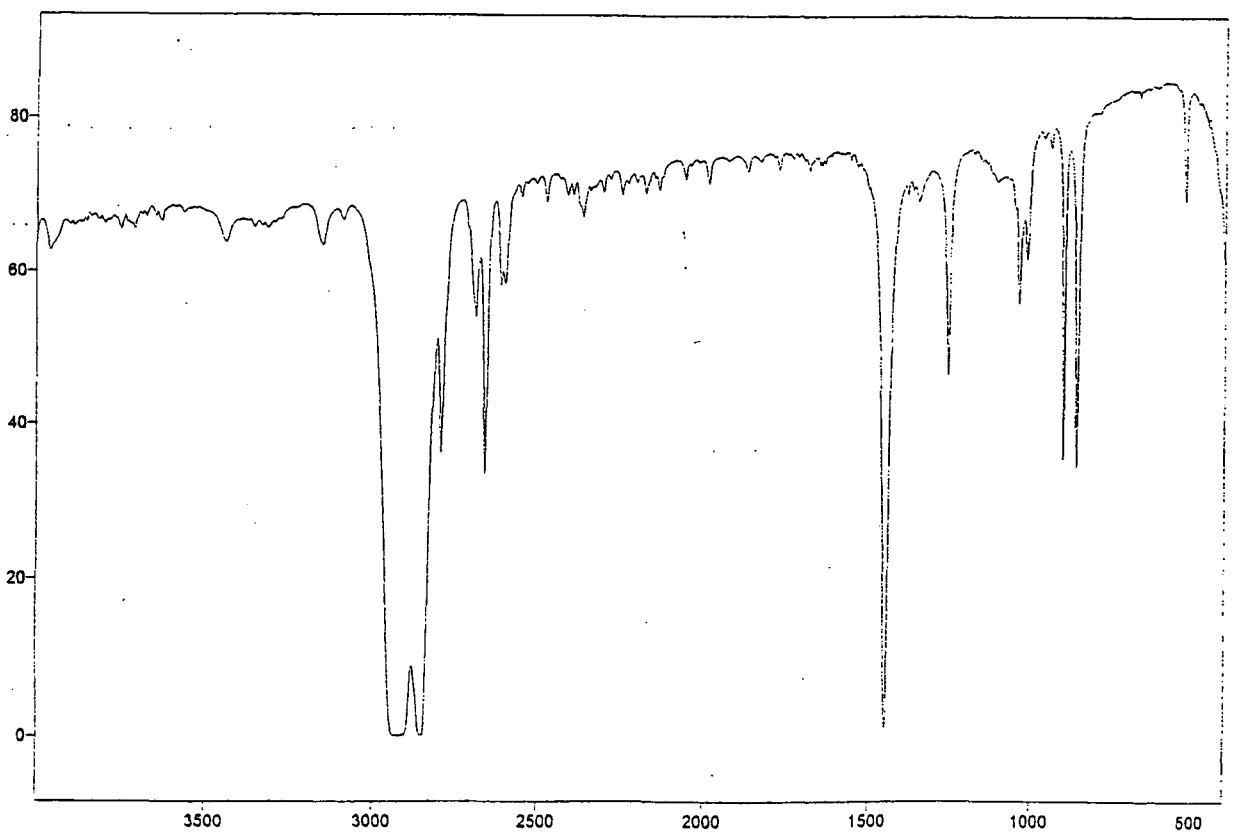
No. 38 2,3-Difluoro-6,7-dimethylquinoxaline (**102**)

No. 39 2,3-Difluoro-6-chloroquinoxaline (**103**)

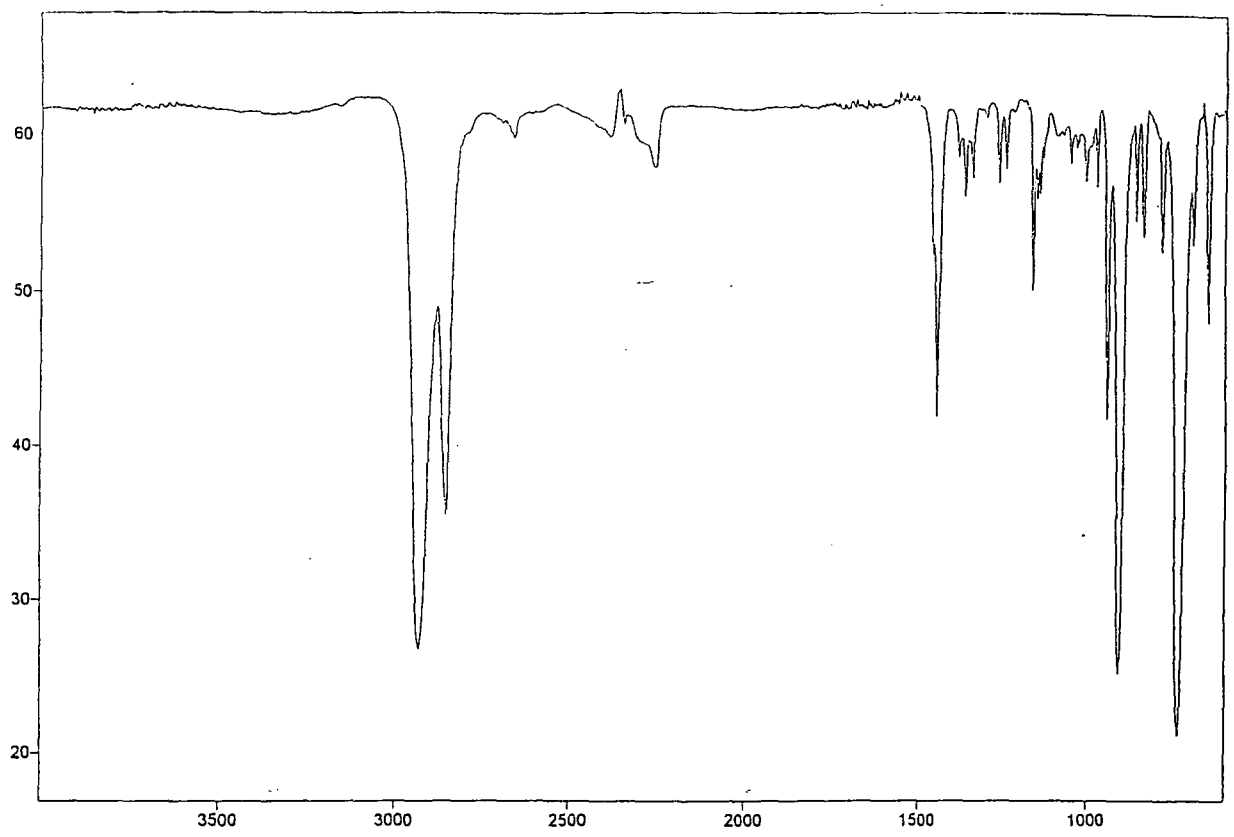
No. 1 Fluorocyclohexane (37)



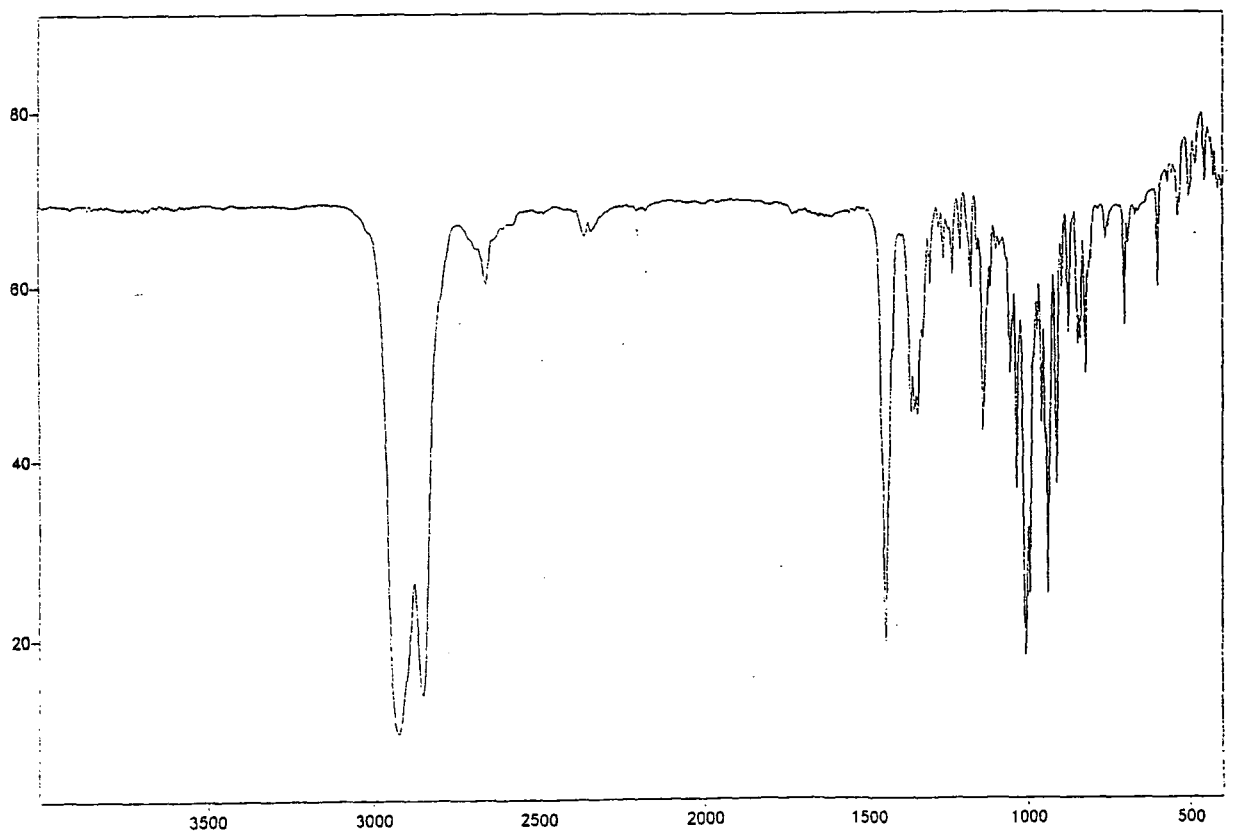
No. 2 *cis*-9-Fluorodecalin (47)



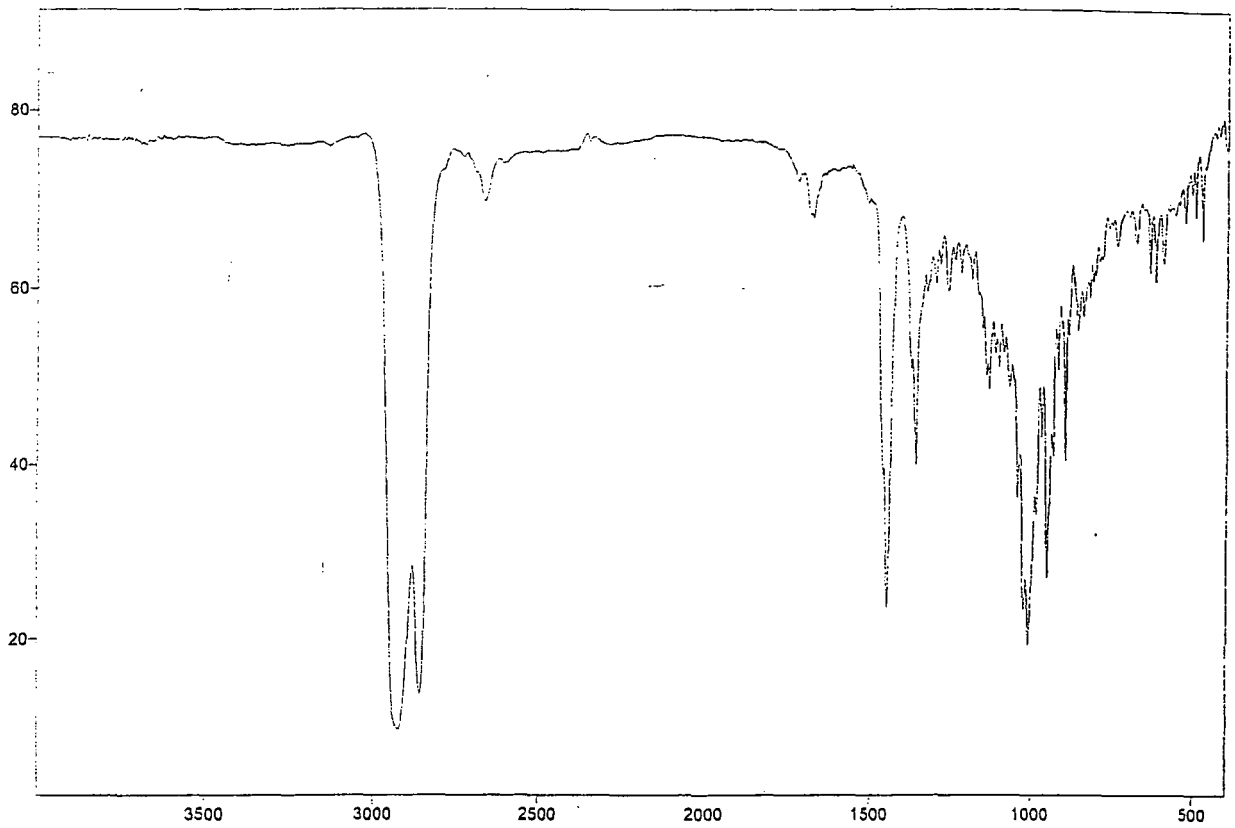
No. 3 *trans*-9-Fluorodecalin (49)



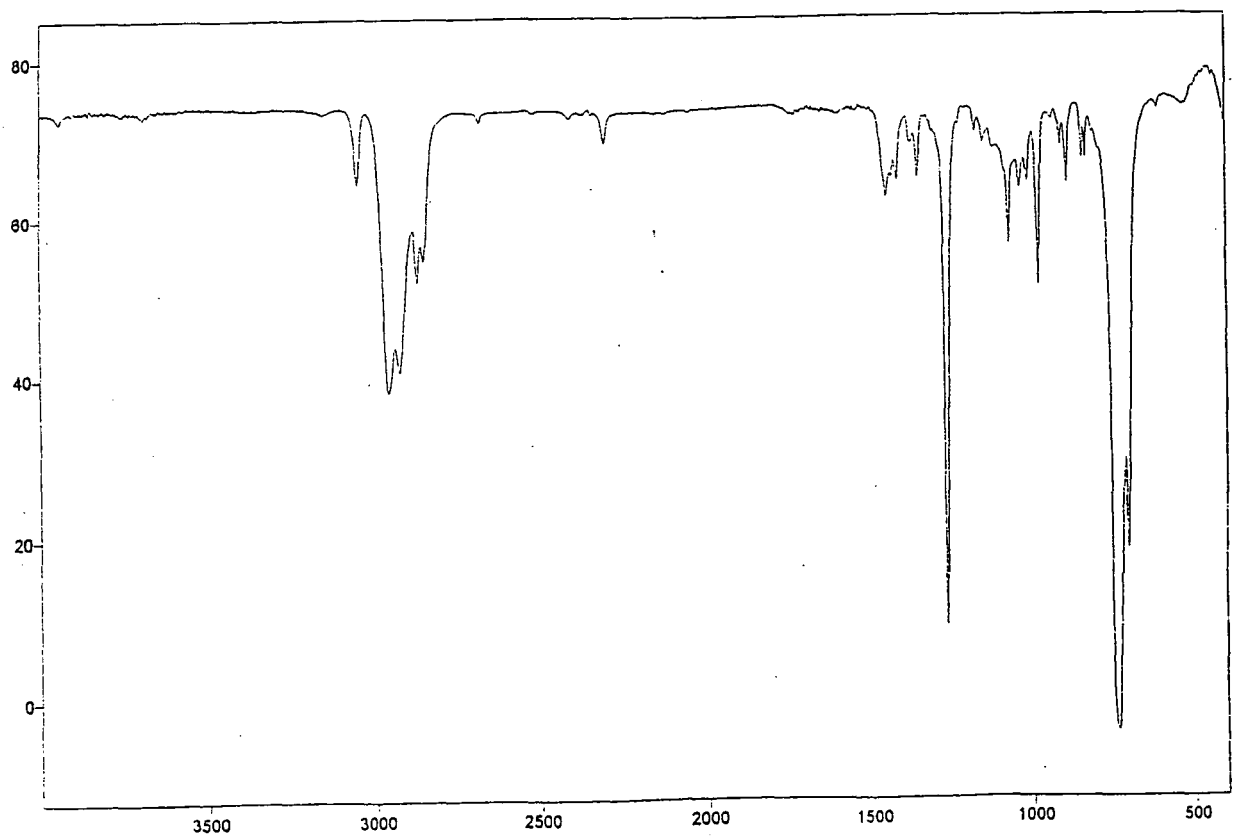
No. 4 *trans*-1- and 2-Fluorodecalin (63A-D)



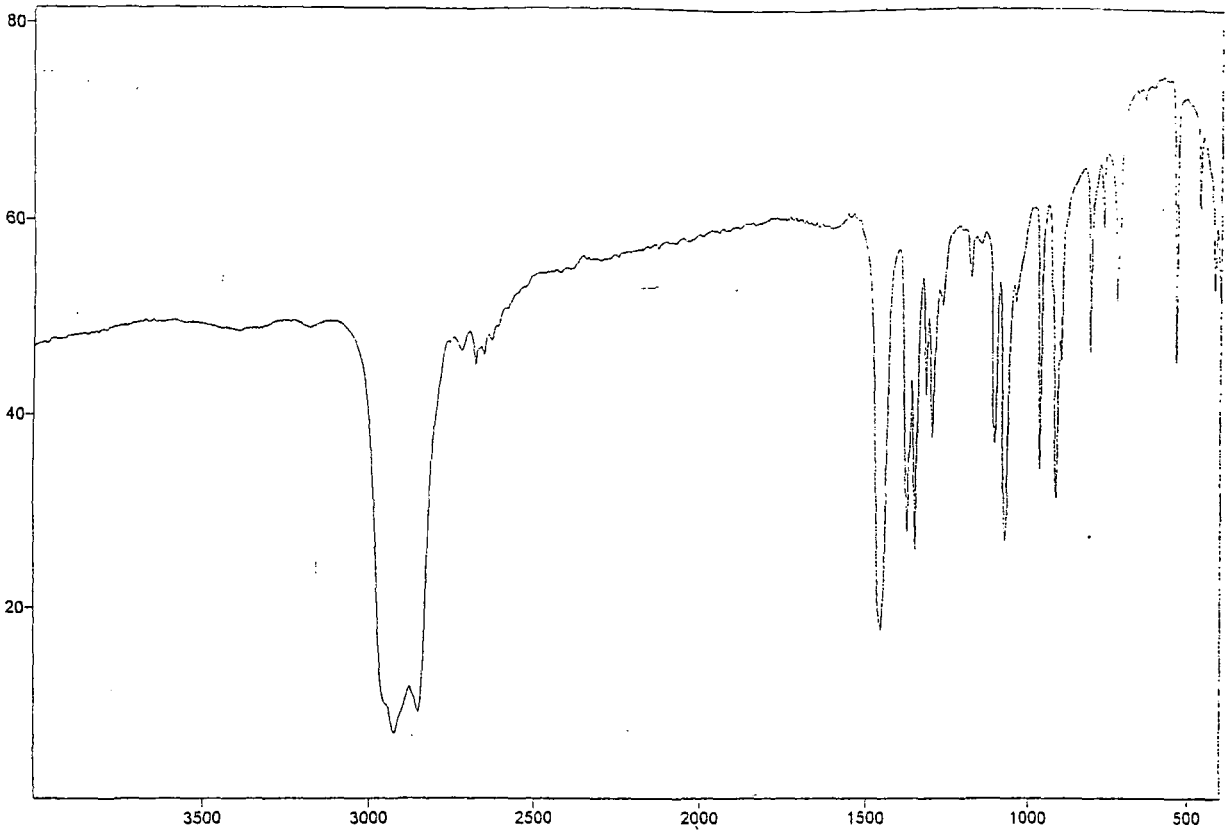
No. 5 *cis*-1- and 2-Fluorodecalin (64A-D)



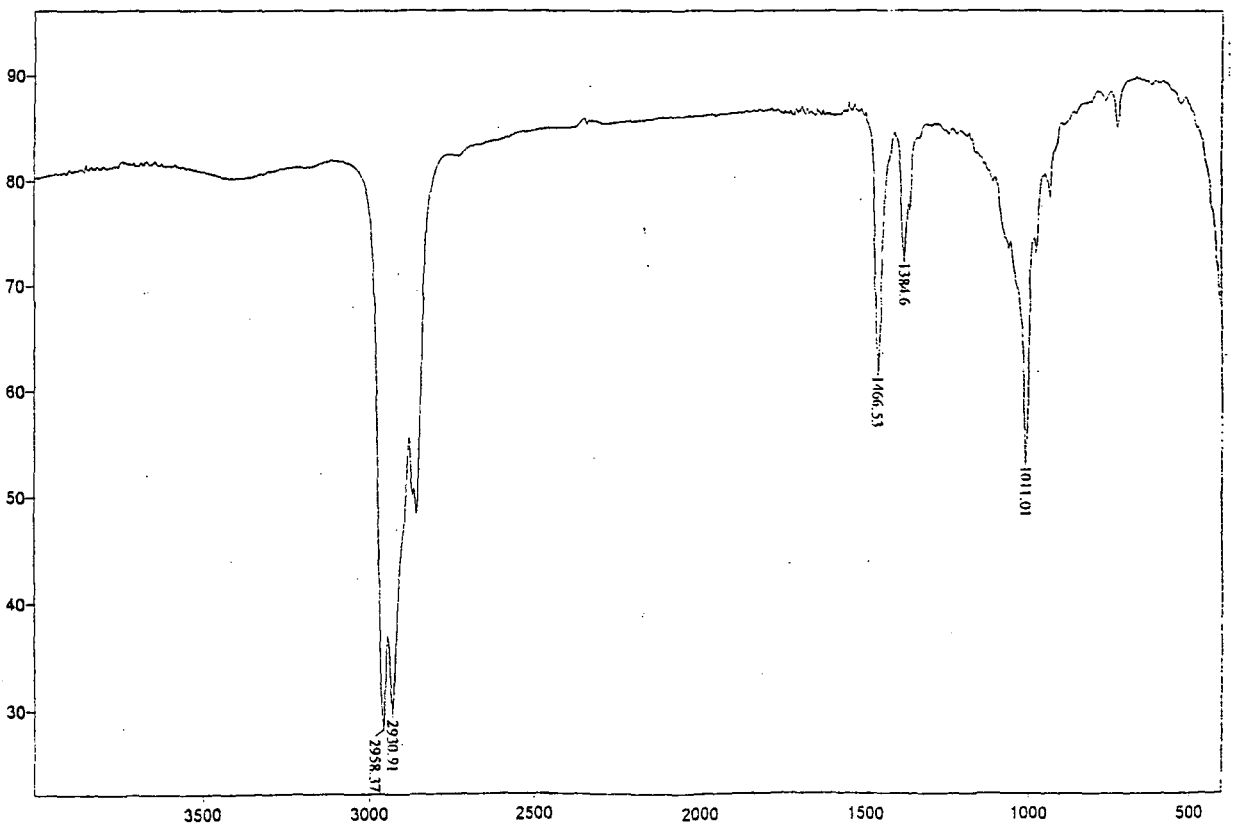
No. 6 *exo*- and *endo*-2-Fluoronorbornane (43A, B)



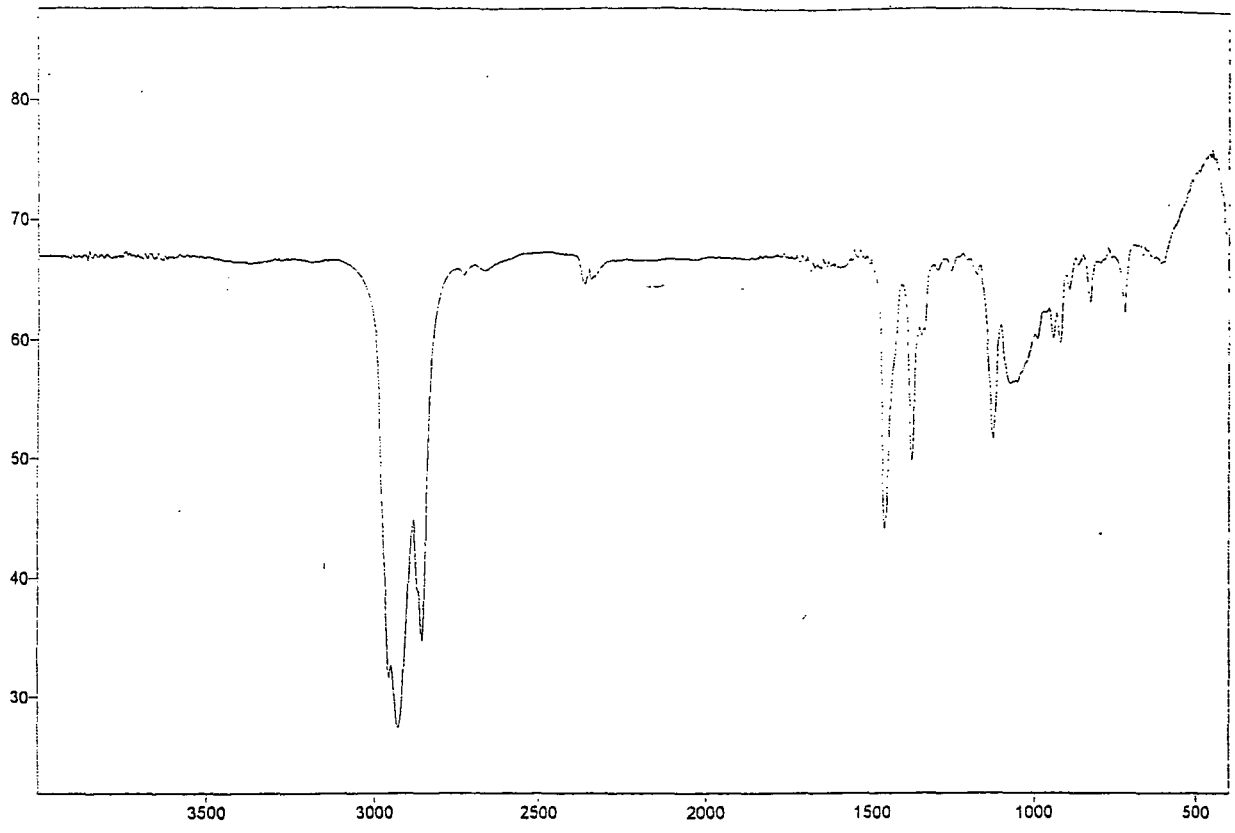
No. 7 1-Fluoroadamantane (44)



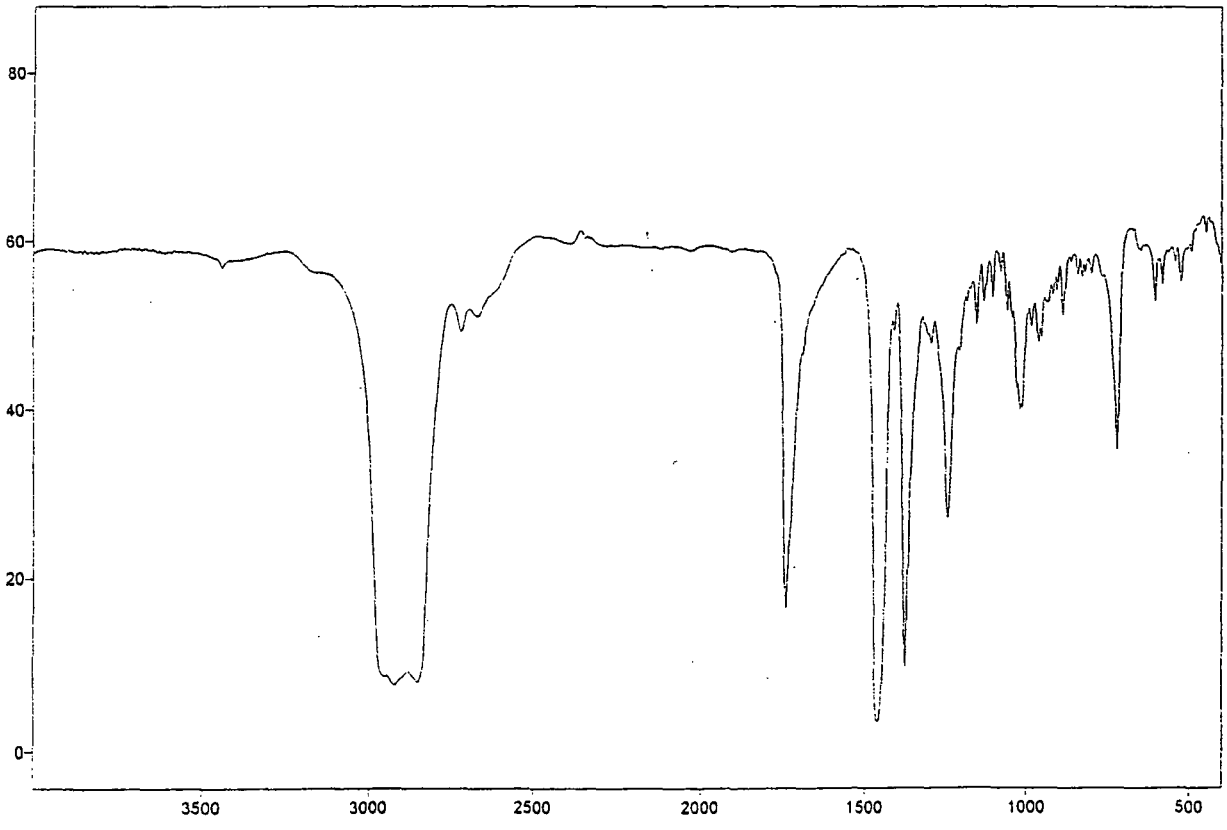
No. 8 1-Fluoro-2-methylheptane (51A) and
1-Fluoro-6-methylheptane (51B)



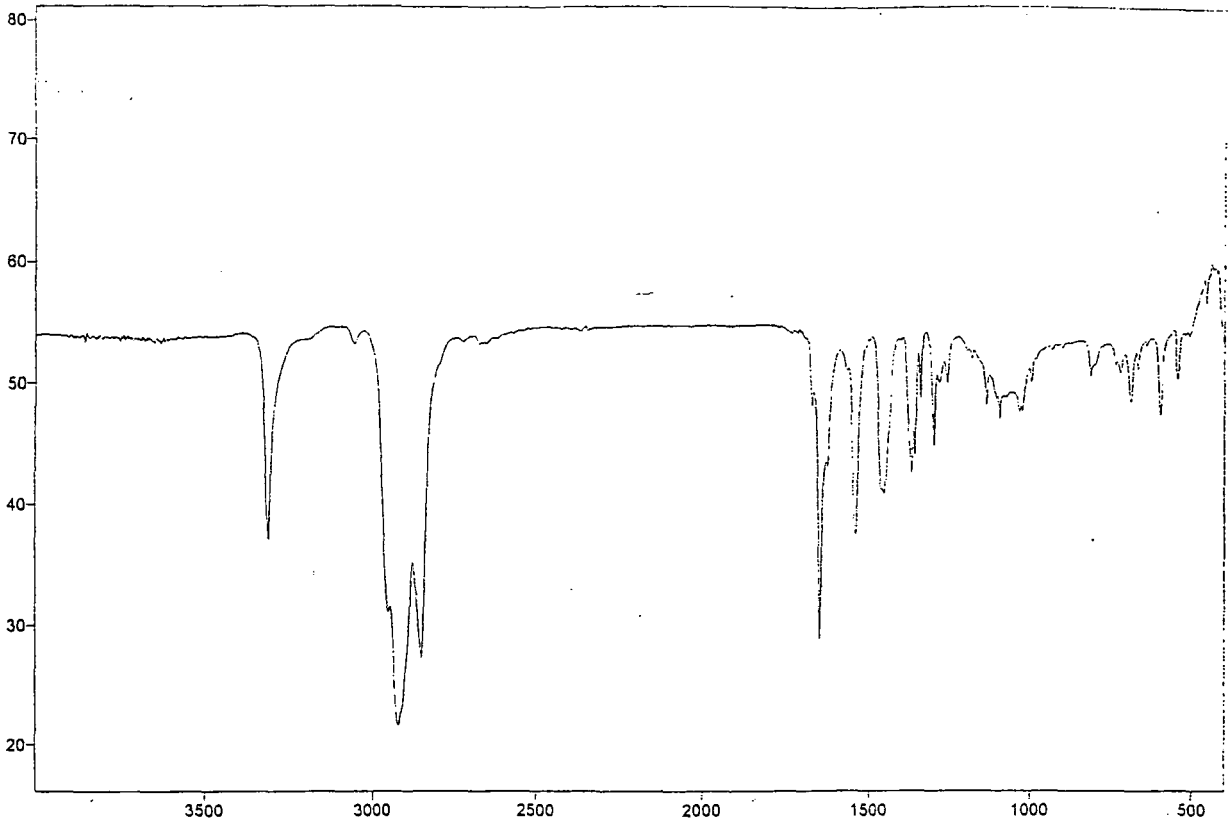
No. 9 2-, 3-, 4-, and 5-Fluorodecane (53A-D)



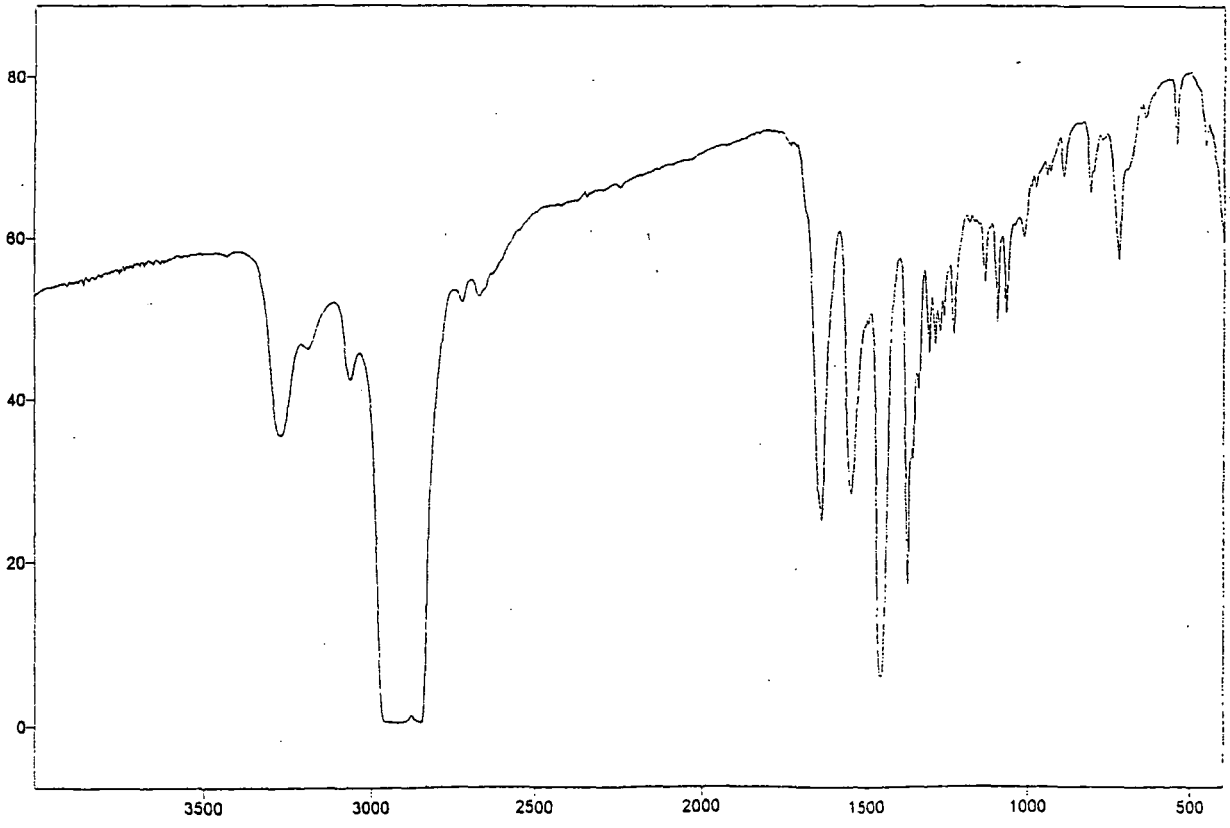
No. 10 3β-Acetoxy-5α-androstanone (55)



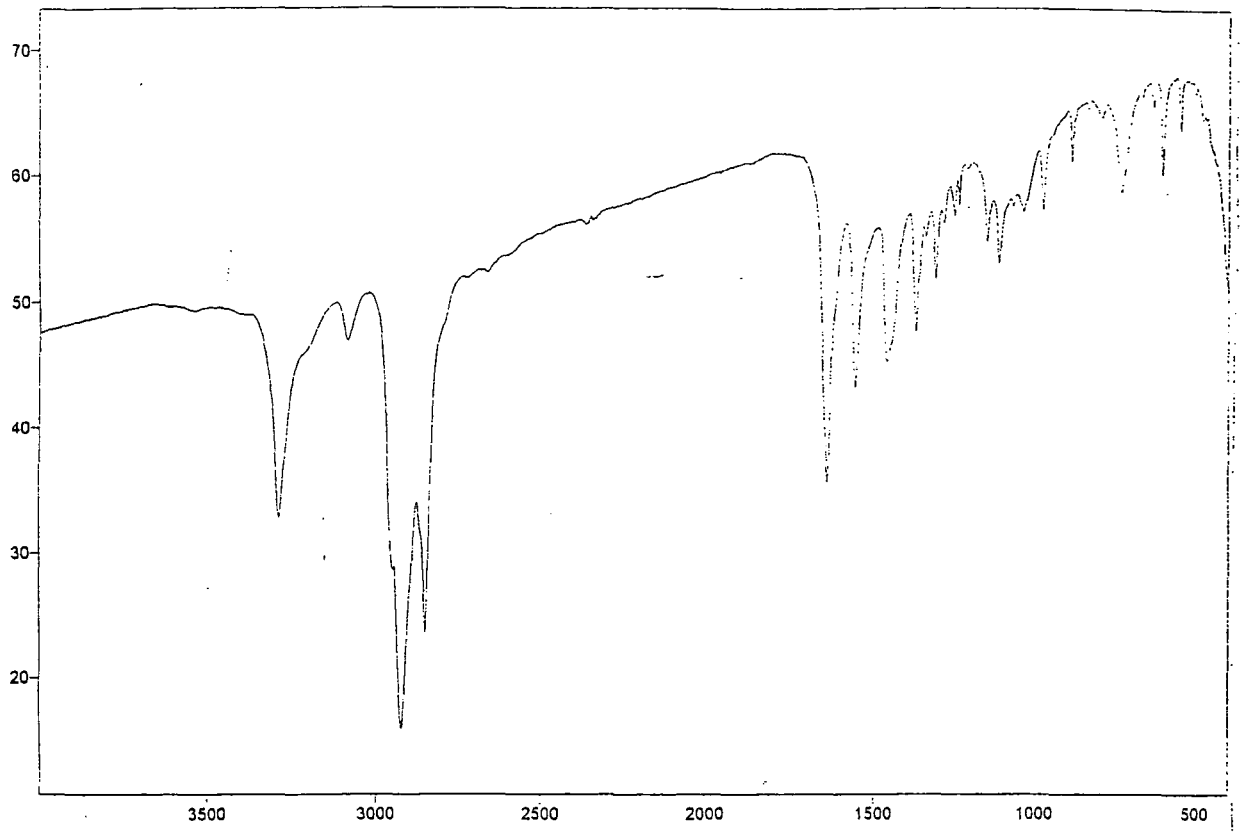
No. 11 N-(1-Adamantyl)acetamide (65)



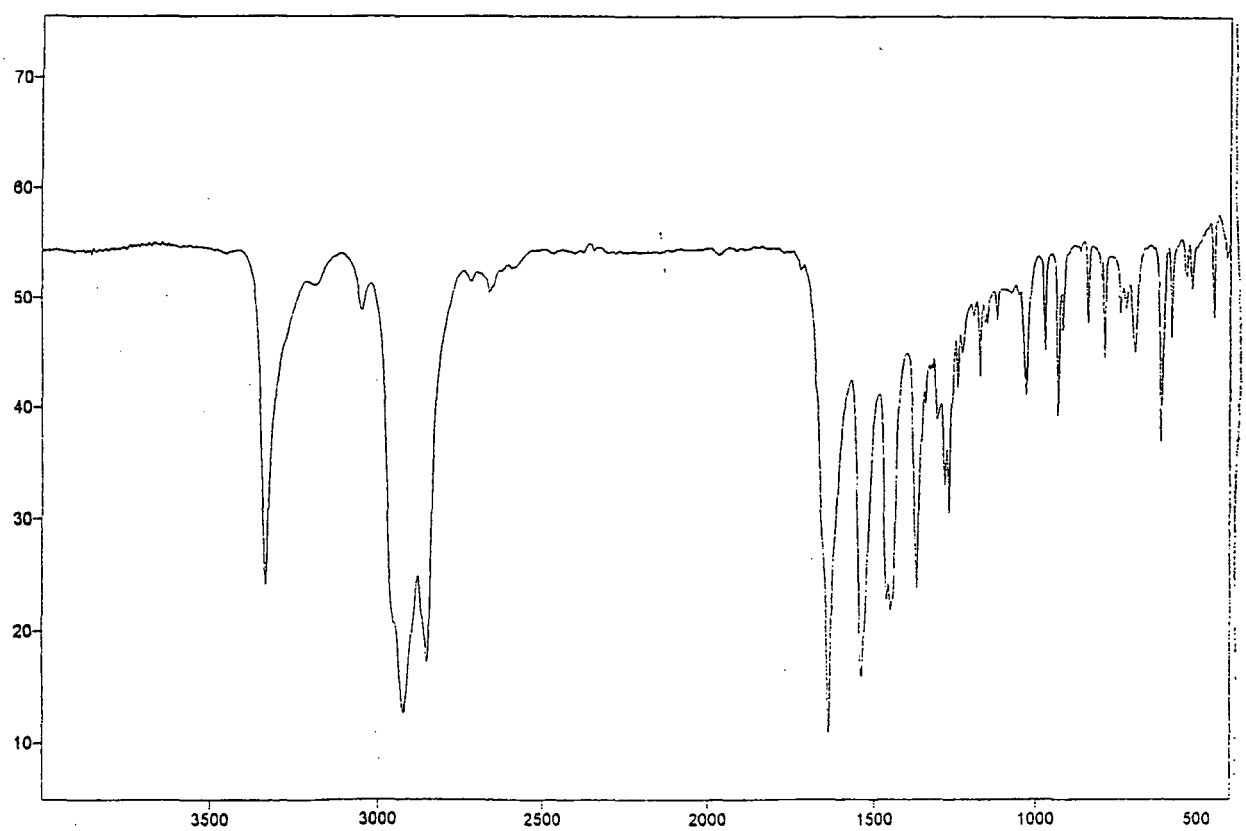
No. 12 N-(1-Adamantyl)propylamide (66)



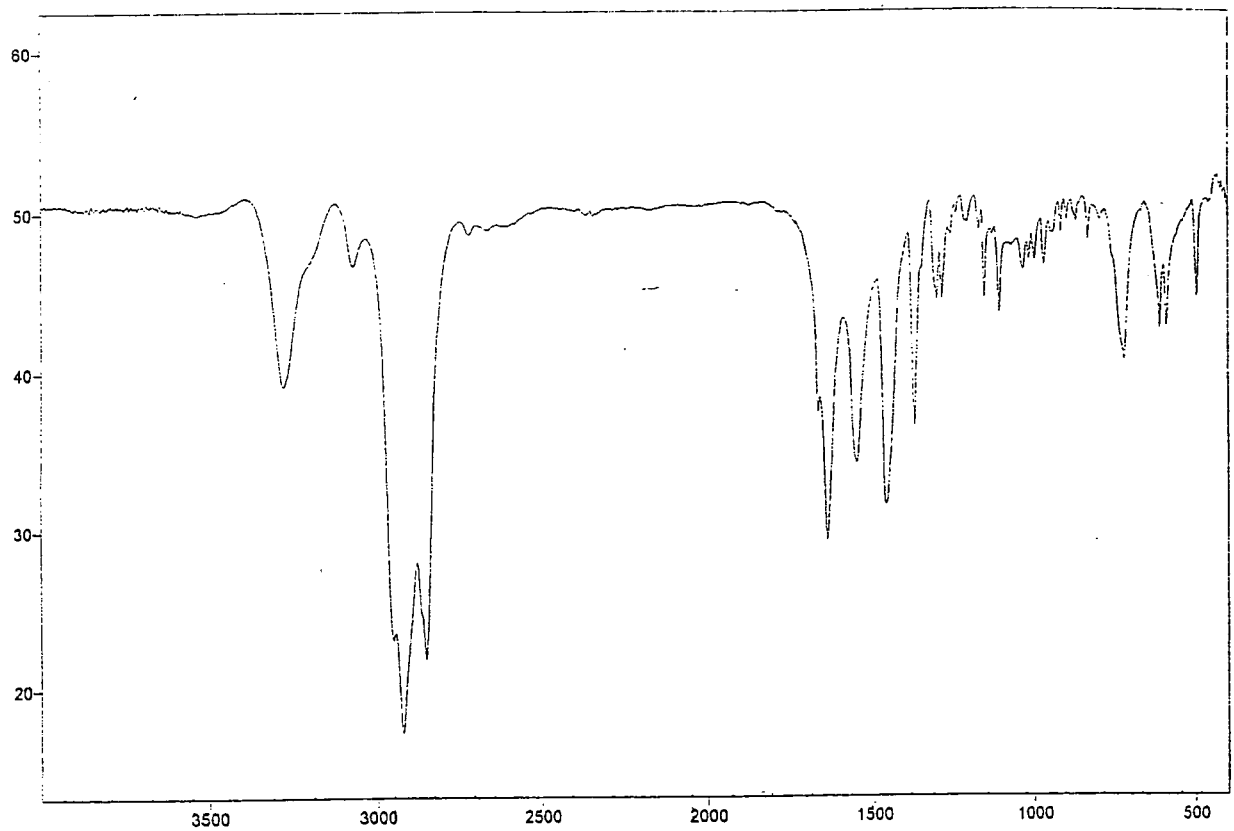
No. 13 N-(Cyclohexyl)acetamide (67)



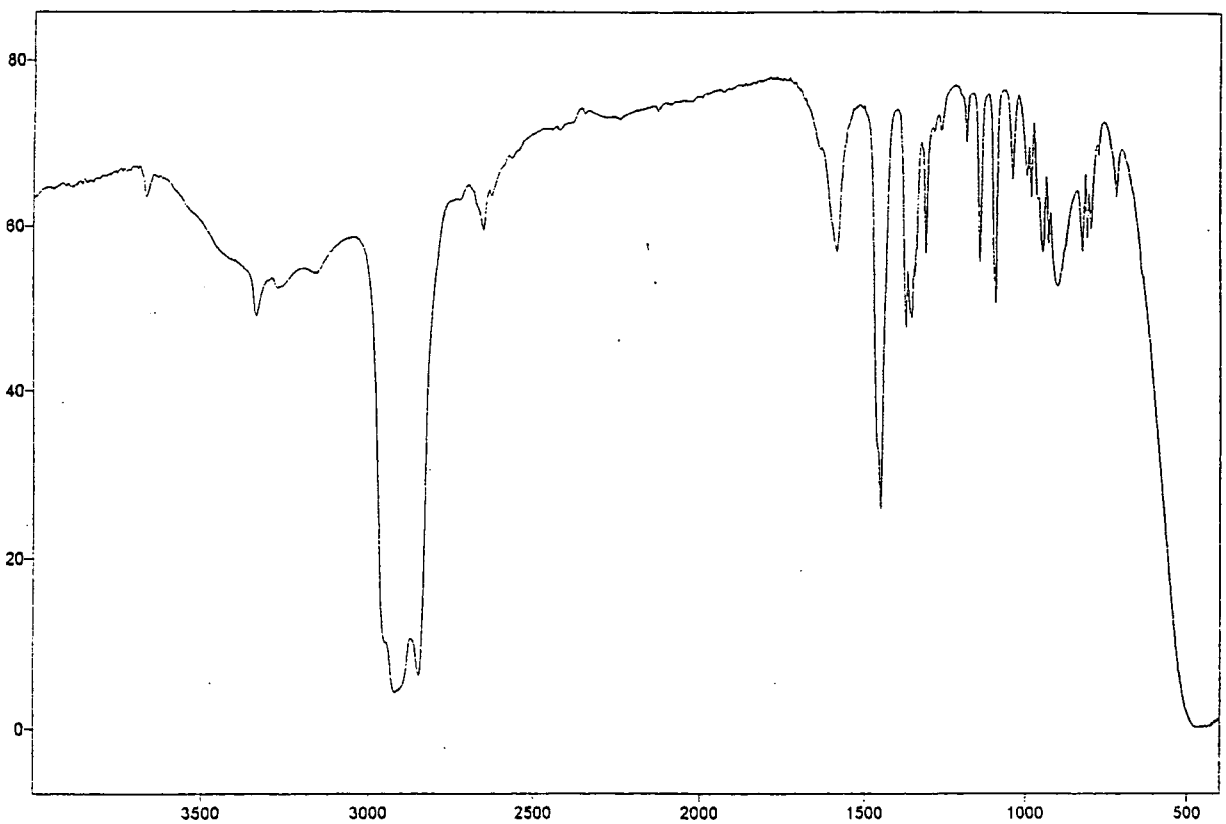
No. 14 N-(*trans*-9-Decalyl)acetamide (68)



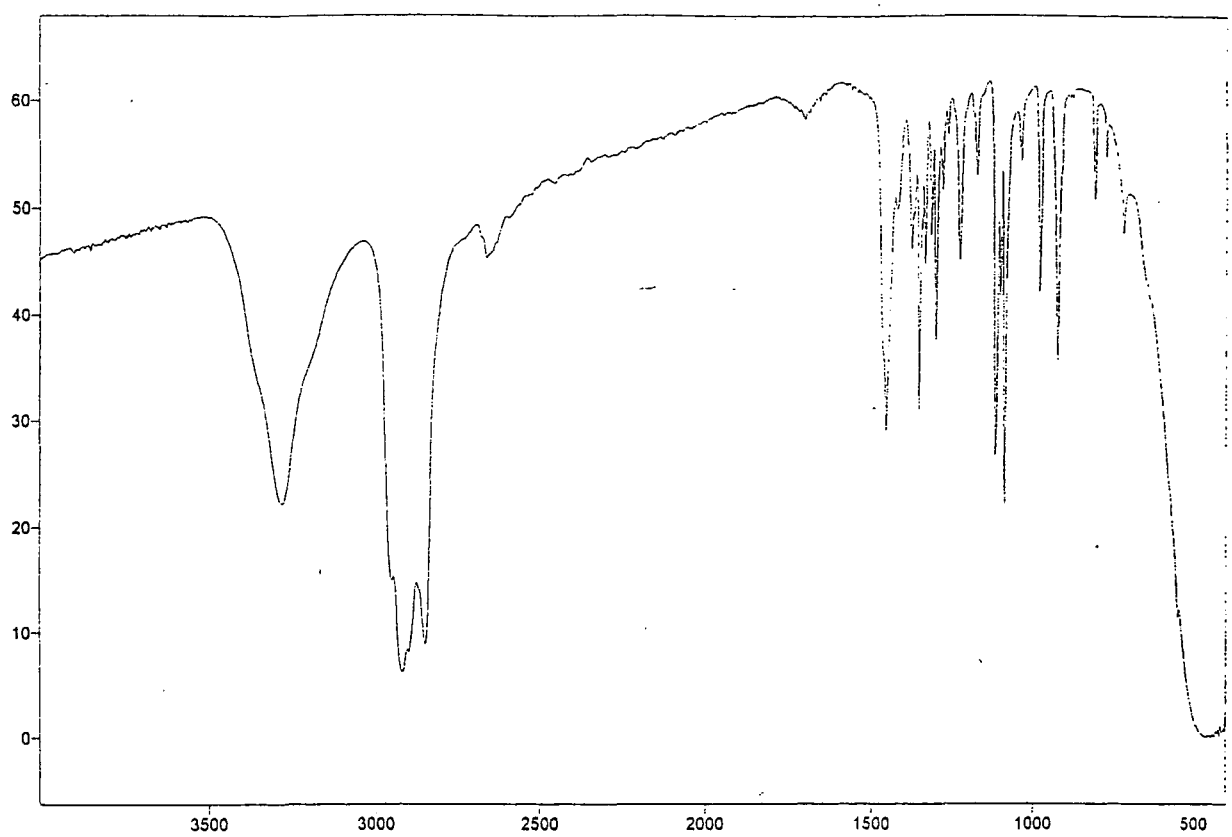
No. 15 N-(*exo*-2-Norbornyl)acetamide (69)



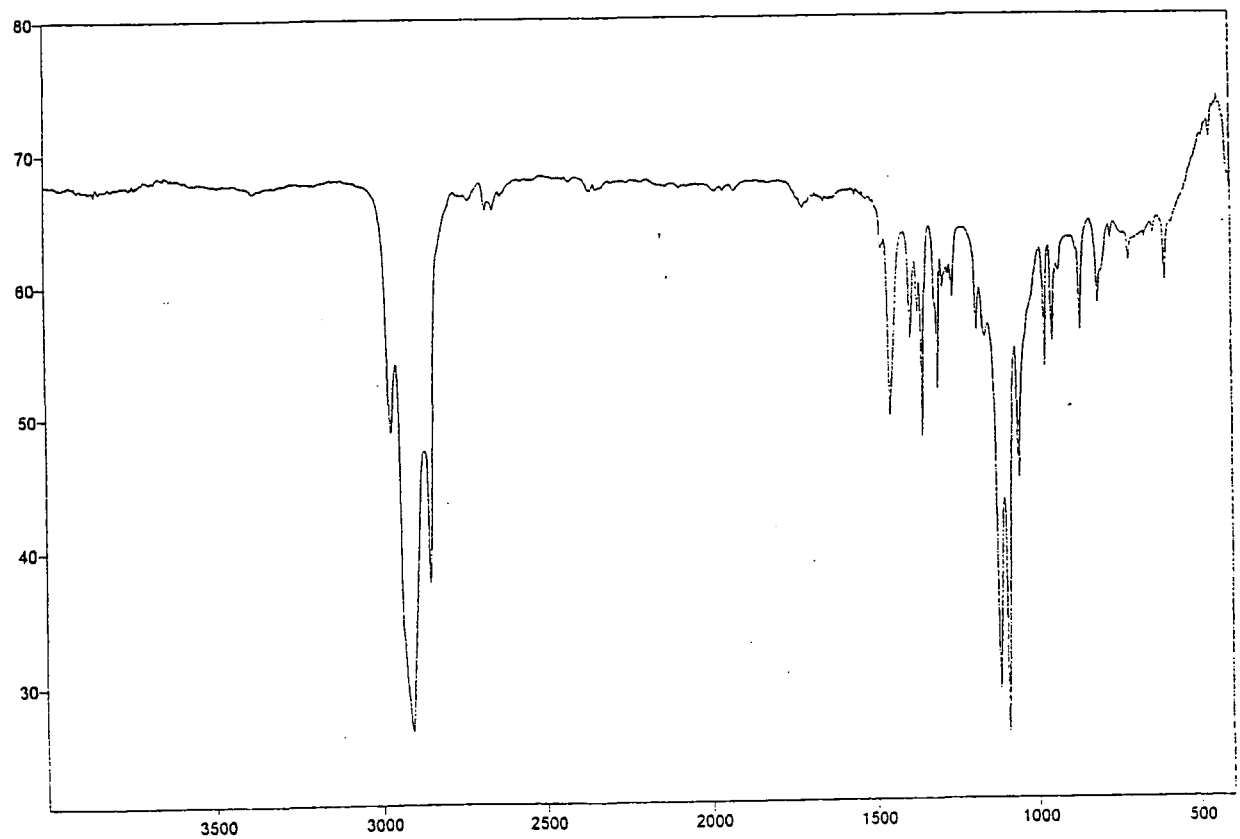
No. 16 1-Aminoadamantane (70)



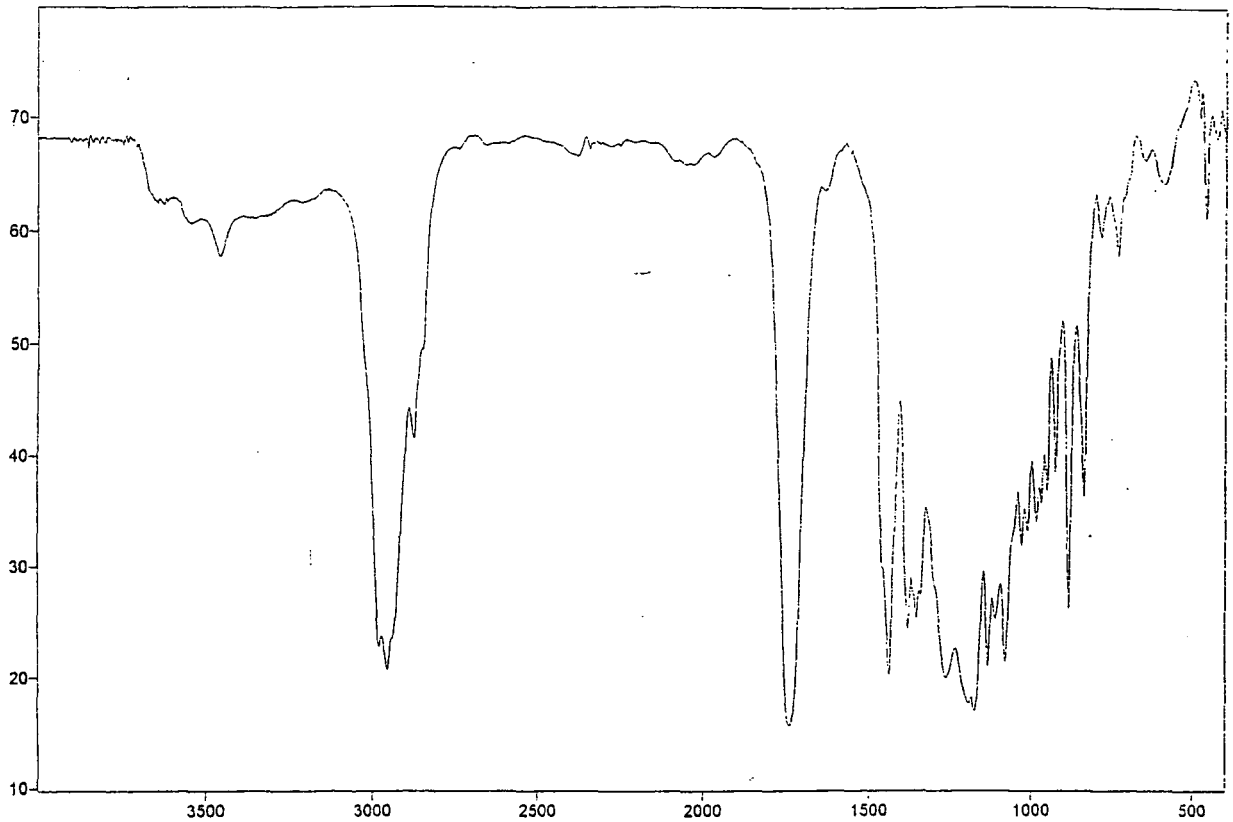
No. 17 1-Hydroxyadamantane (71)



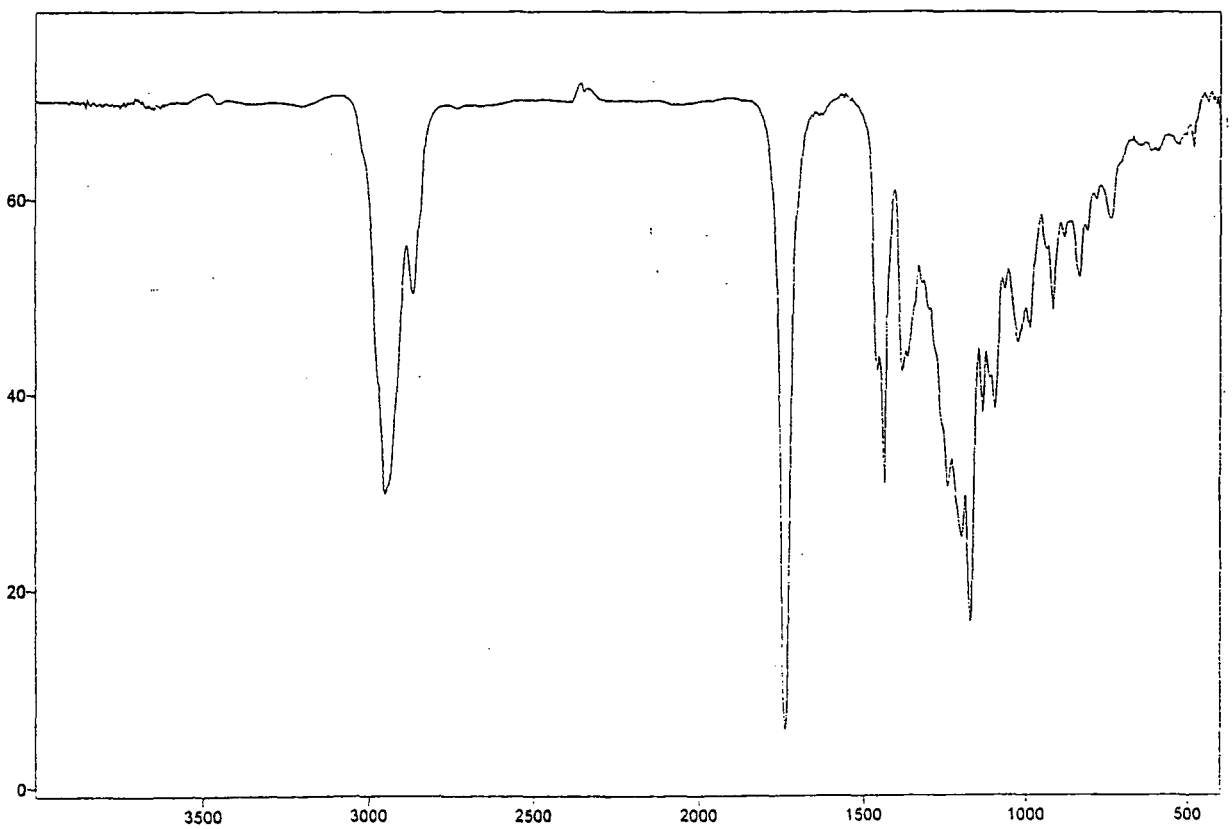
No. 18 1-Ethoxyadamantane (72)



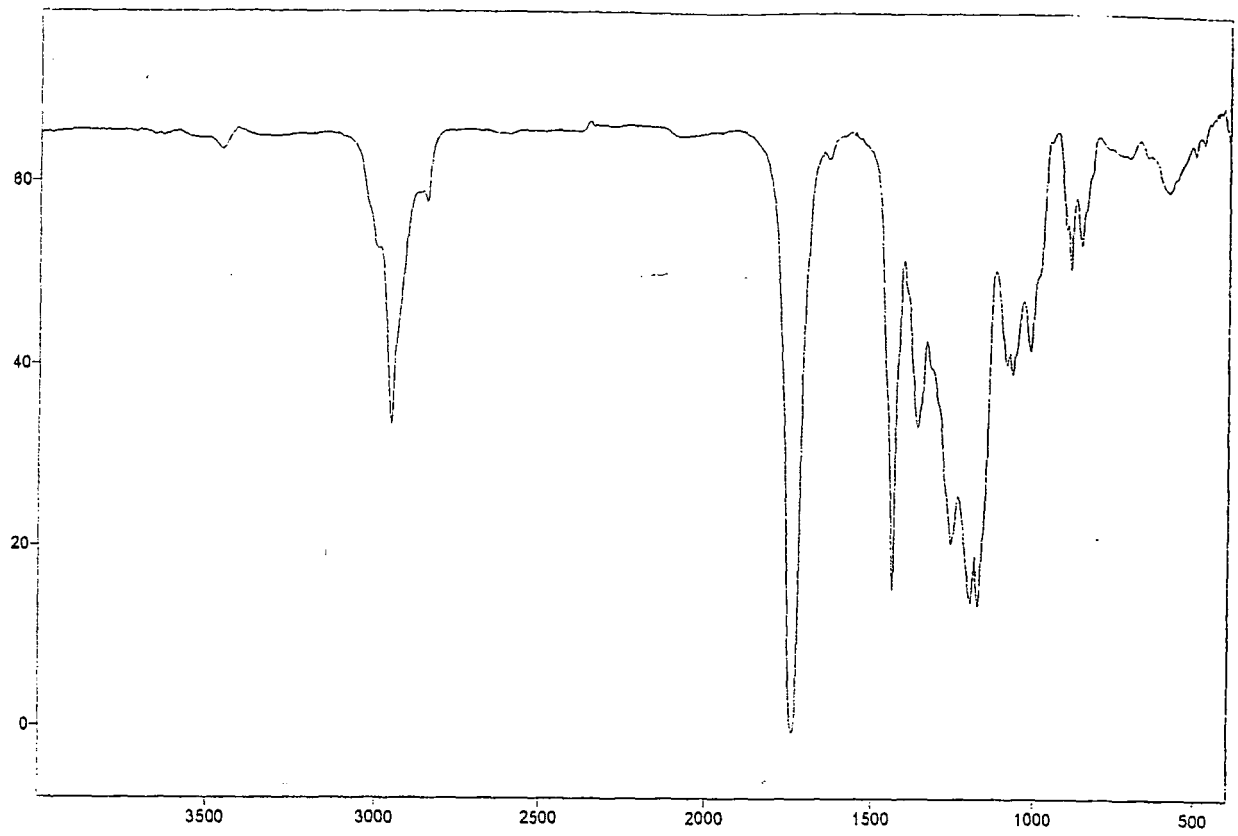
No. 19 Methyl 3-fluorovalerate (74A) and
Methyl 4-fluorovalerate (74B)



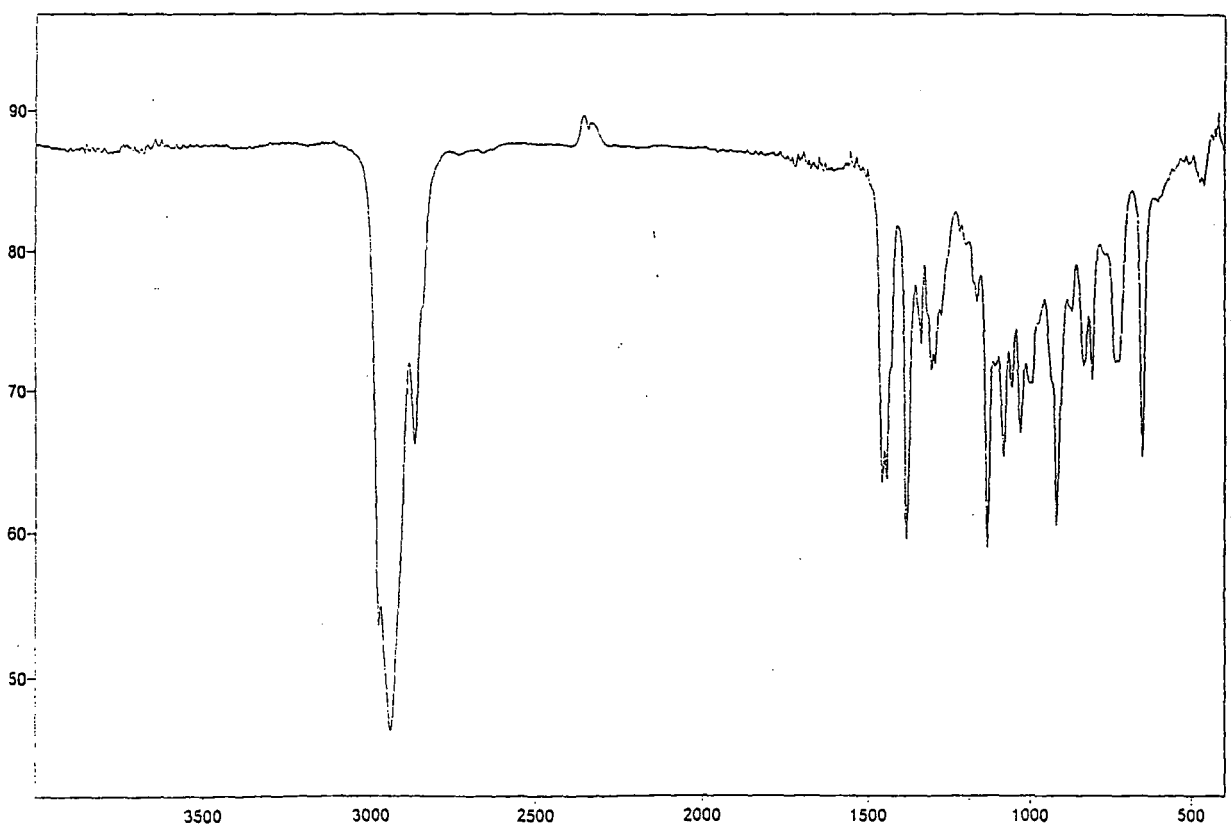
No. 20 Methyl 3-, 4-, 5-, and 6-fluoroenanthate (76A-D)



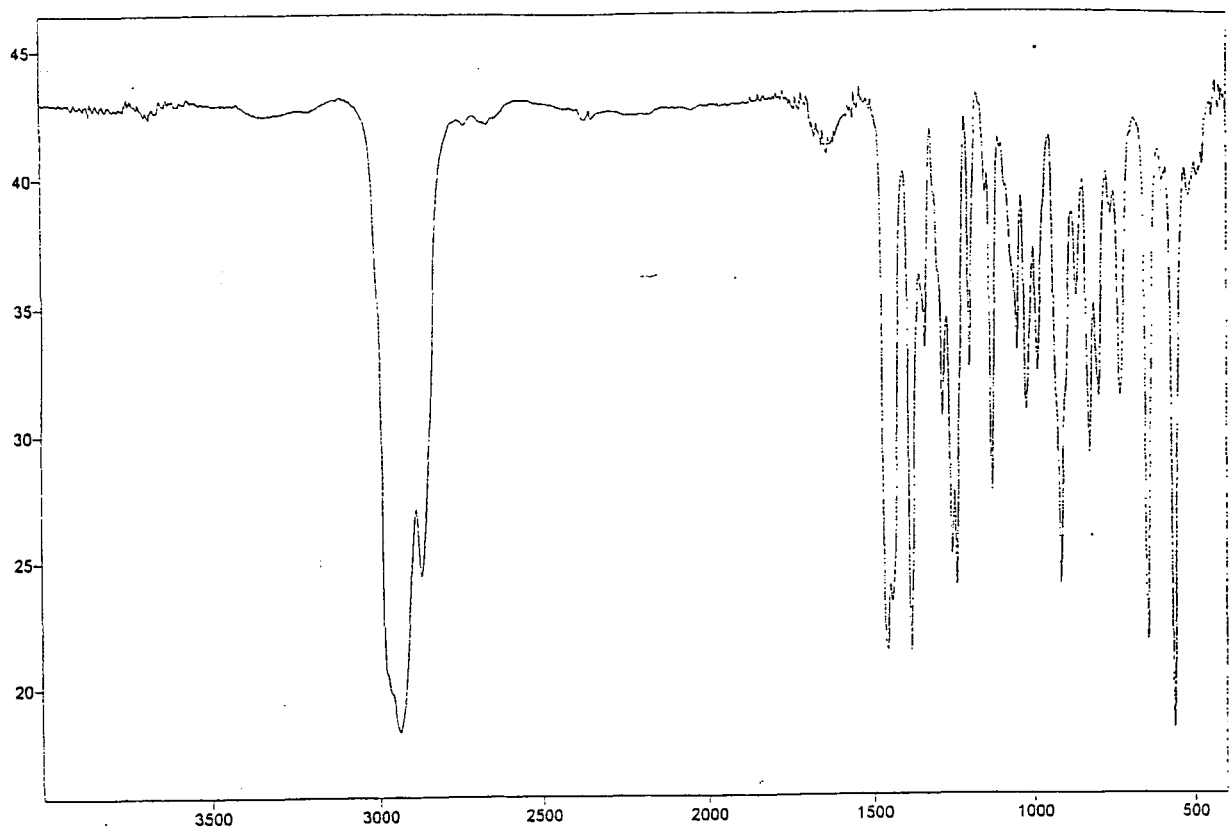
No. 21 Dimethyl 3-fluoropimelate (79A) and
Dimethyl 4-fluoropimelate (79B)



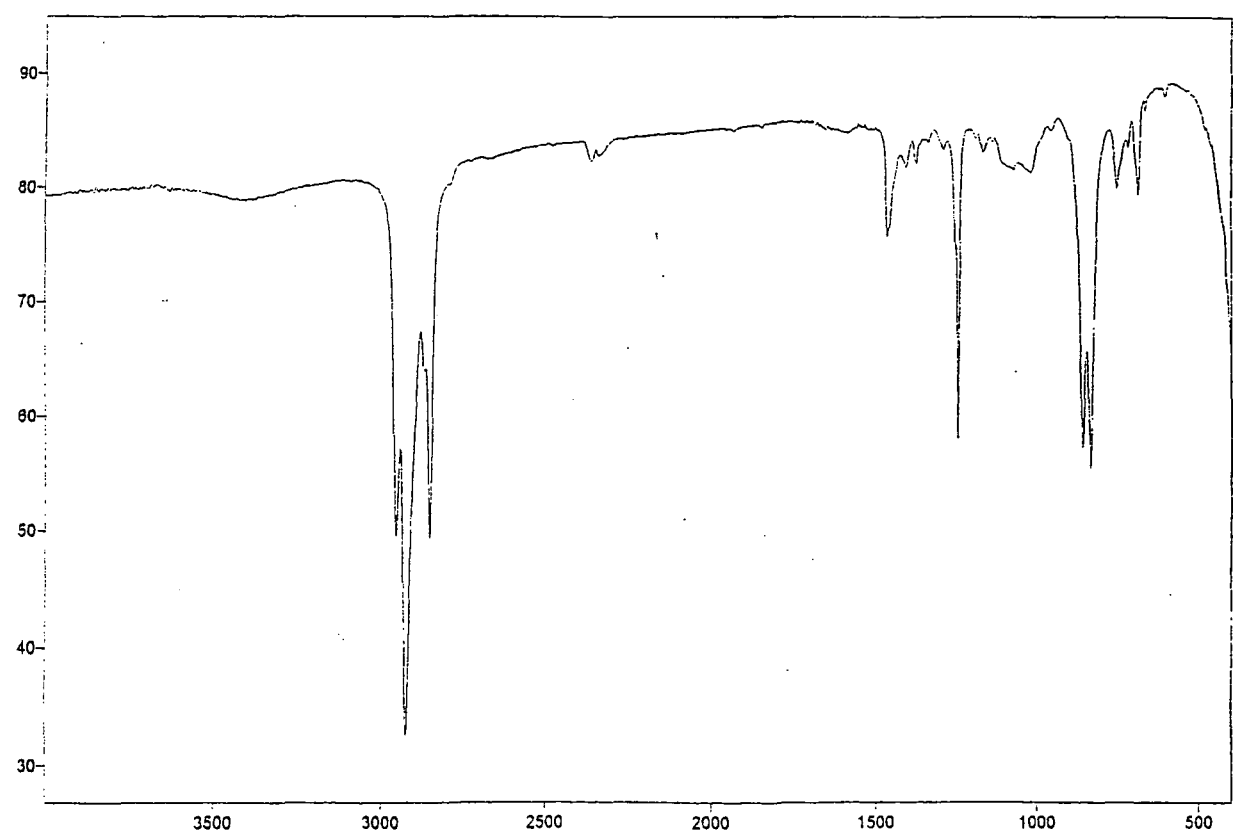
No. 22 1-Chloro-4-fluorohexane (84B) and
1-Chloro-5-fluorohexane (84C)



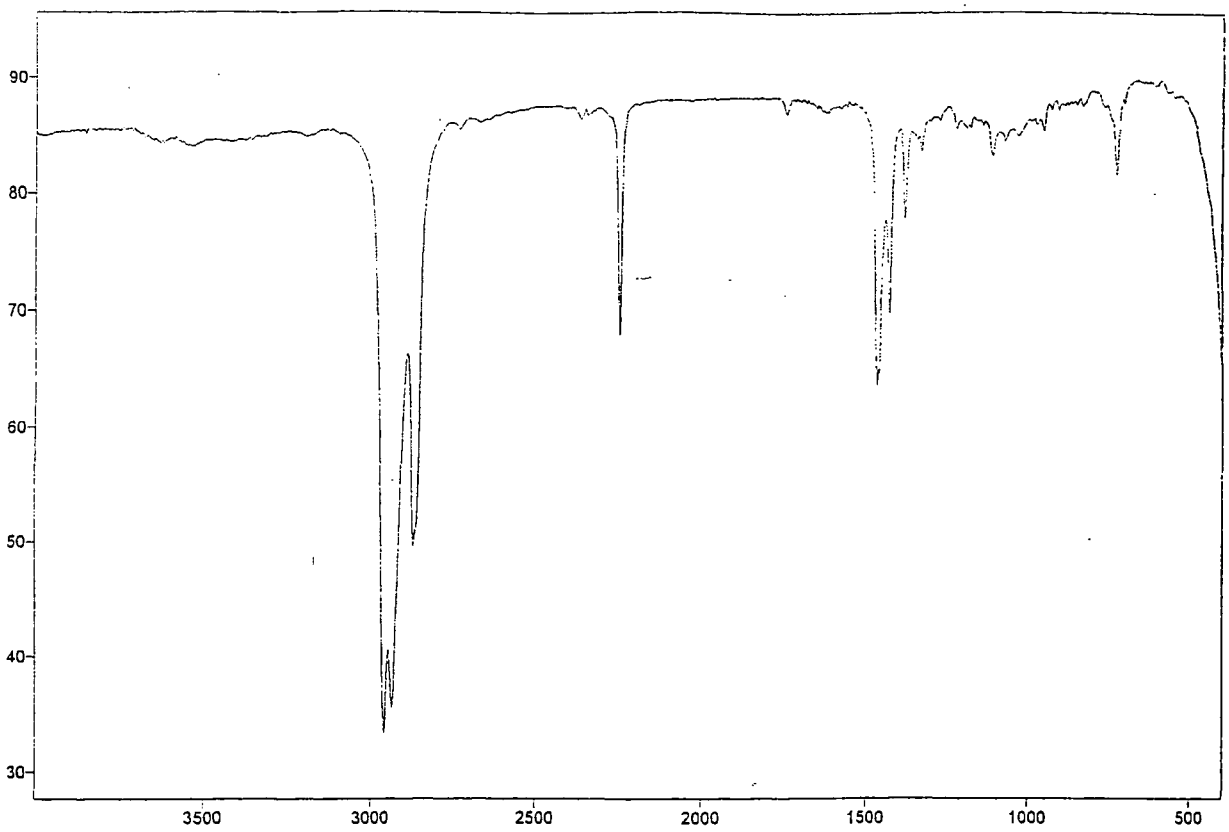
No. 23 1-Bromo-4-fluorohexane (82B) and
1-Bromo-5-fluorohexane (82C)



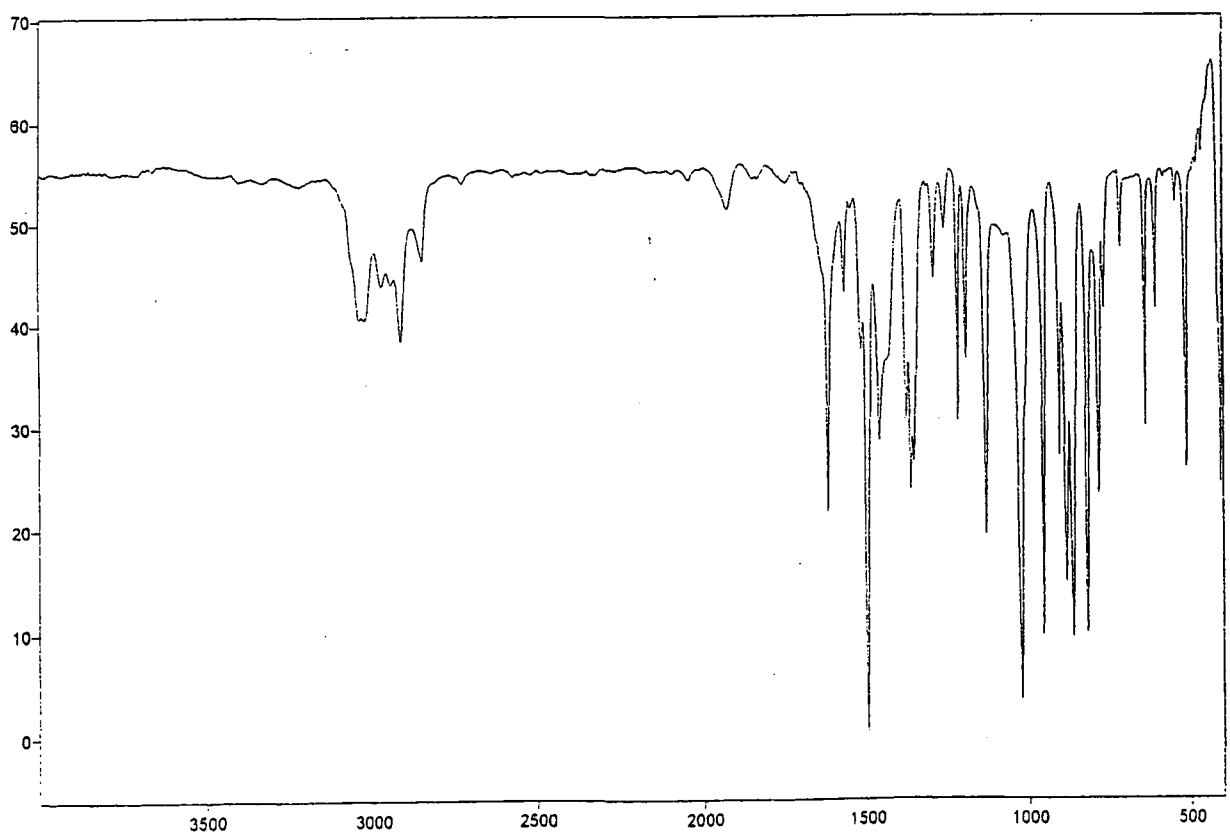
No. 24 Decyltrimethylsilane (85)



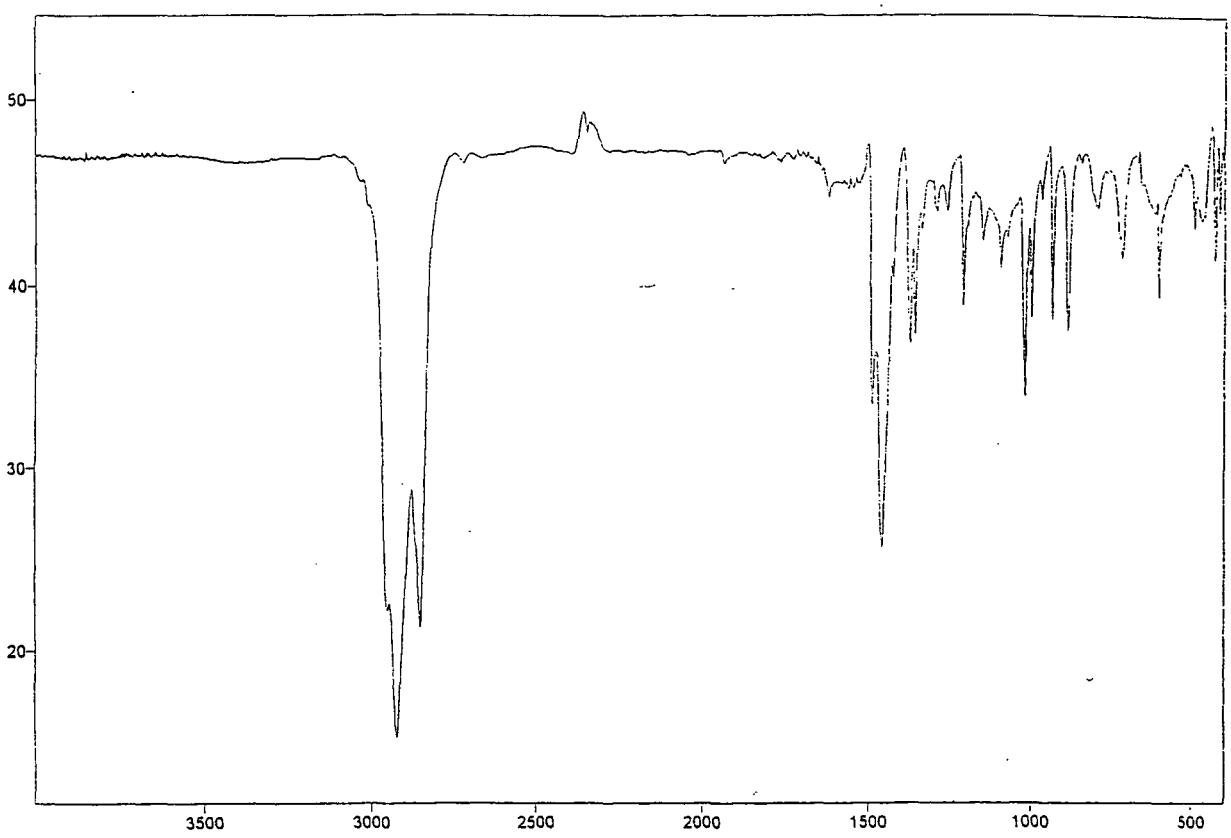
No. 25 Hexanenitrile (87)



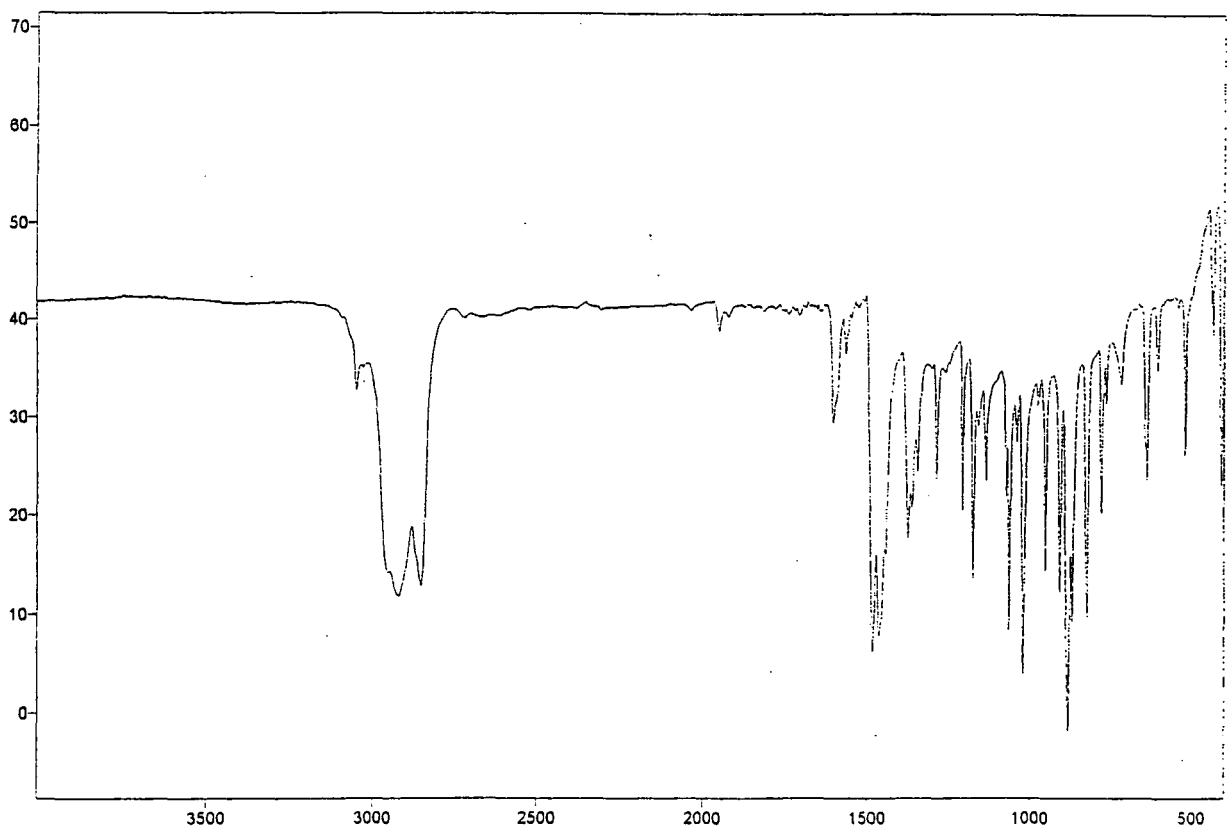
No. 26 6-Methylquinoxaline (88)



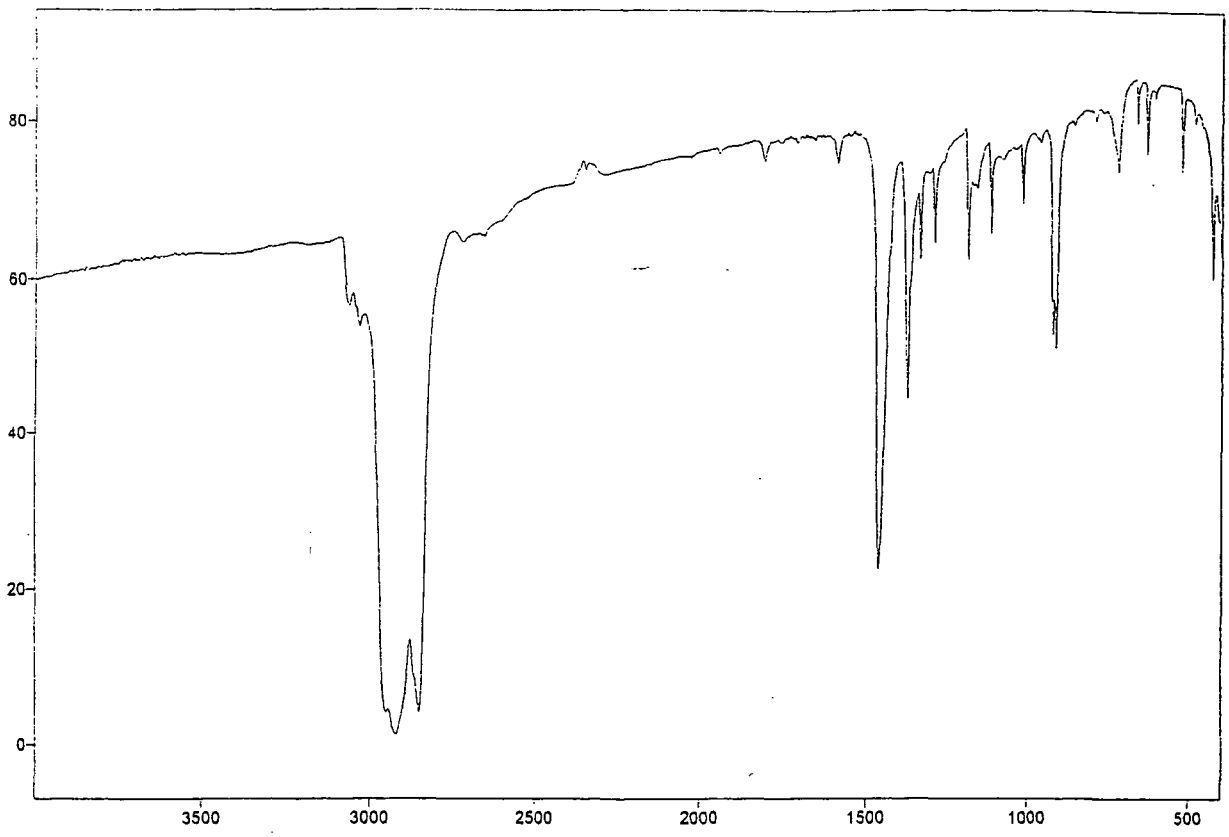
No. 27 6,7-Dimethylquinoxaline (89)



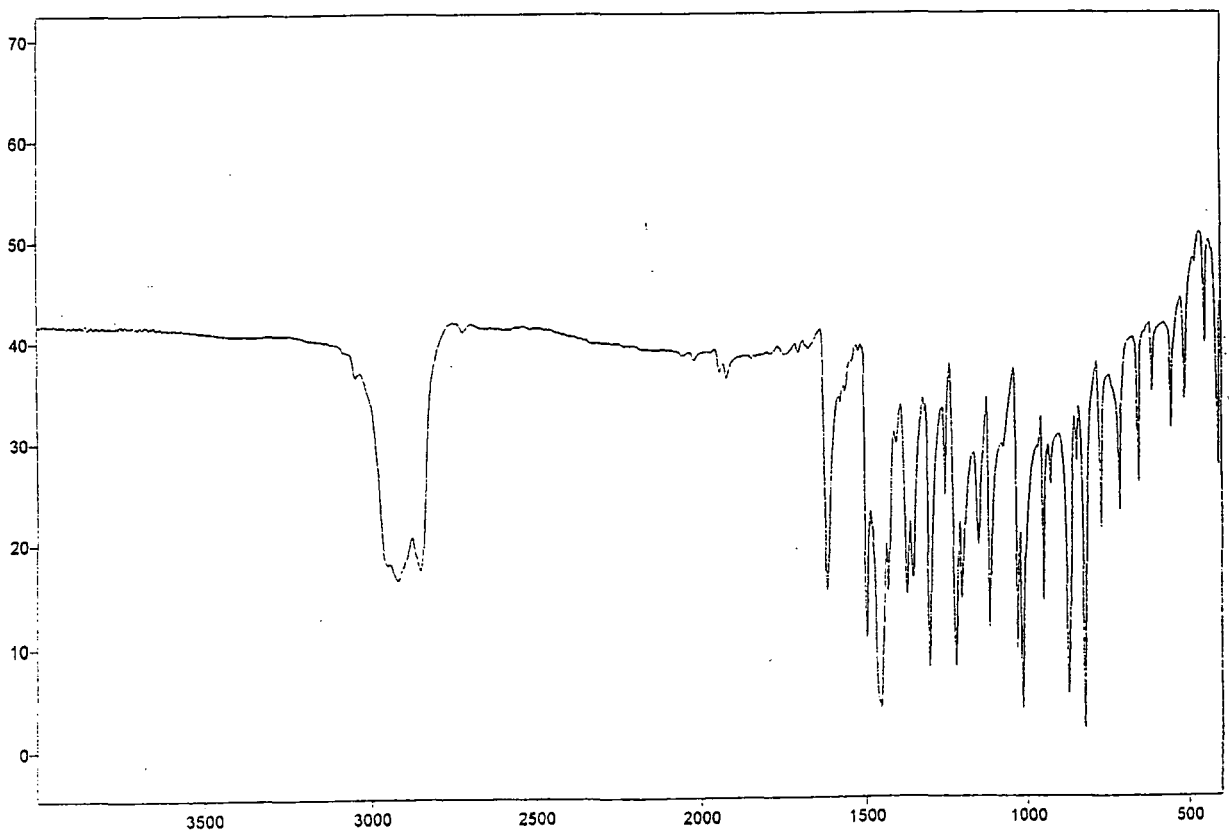
No. 28 6-Chloroquinoxaline (90)



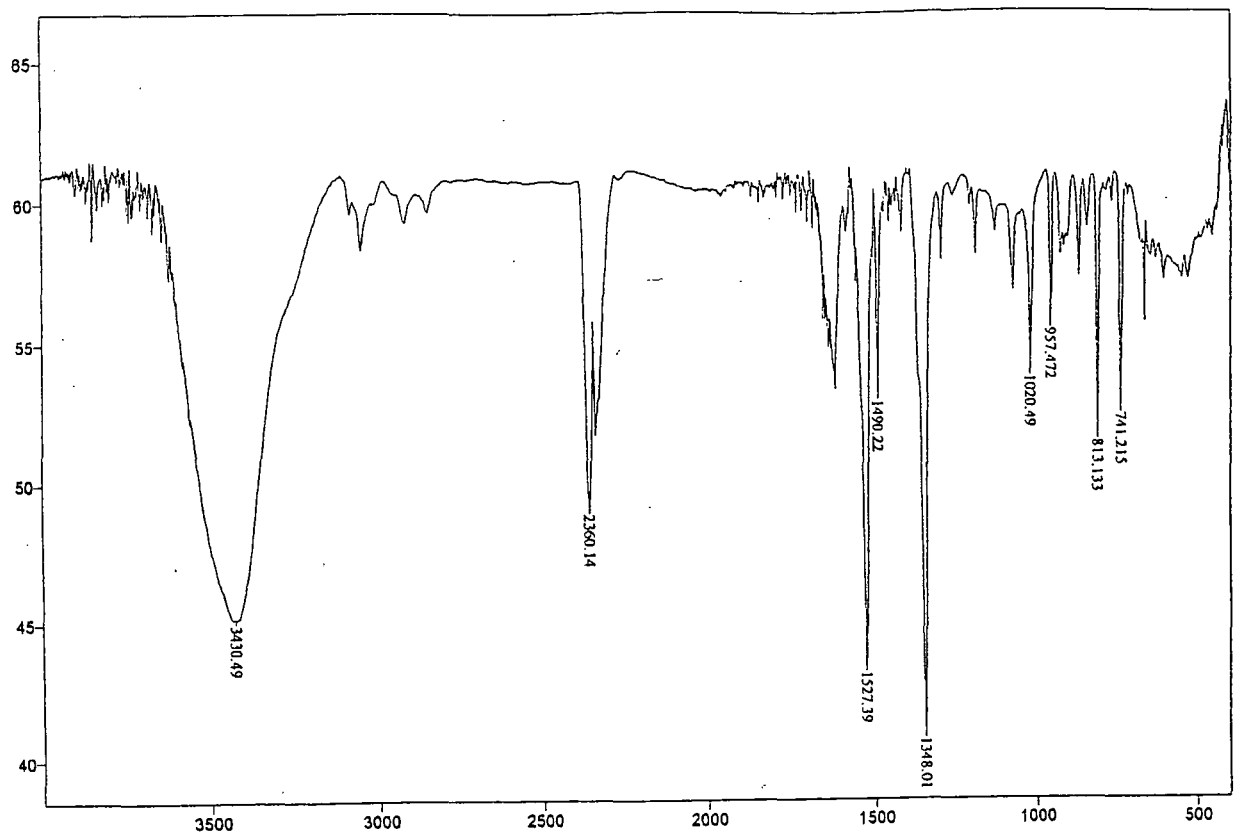
No. 29 6,7-Dichloroquinoxaline (91)



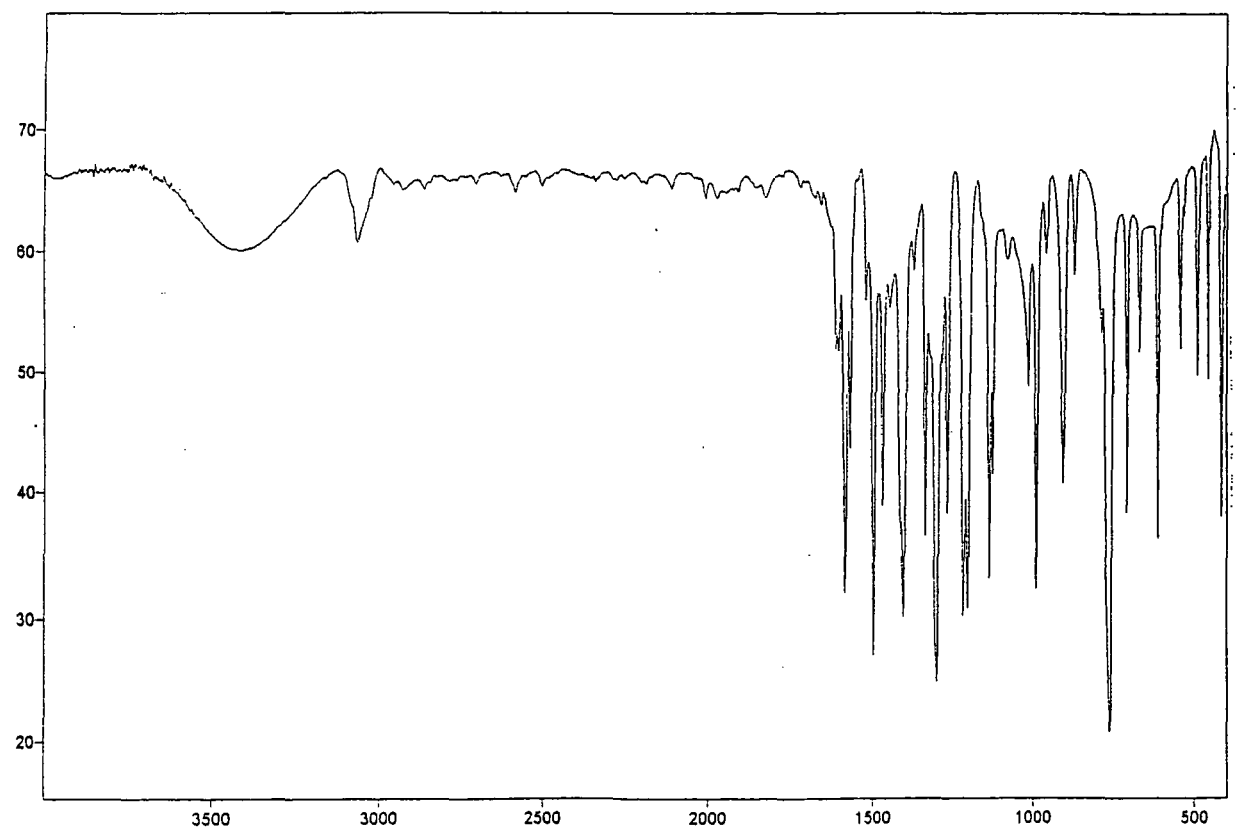
No. 30 6-Methoxyquinoxaline (92)



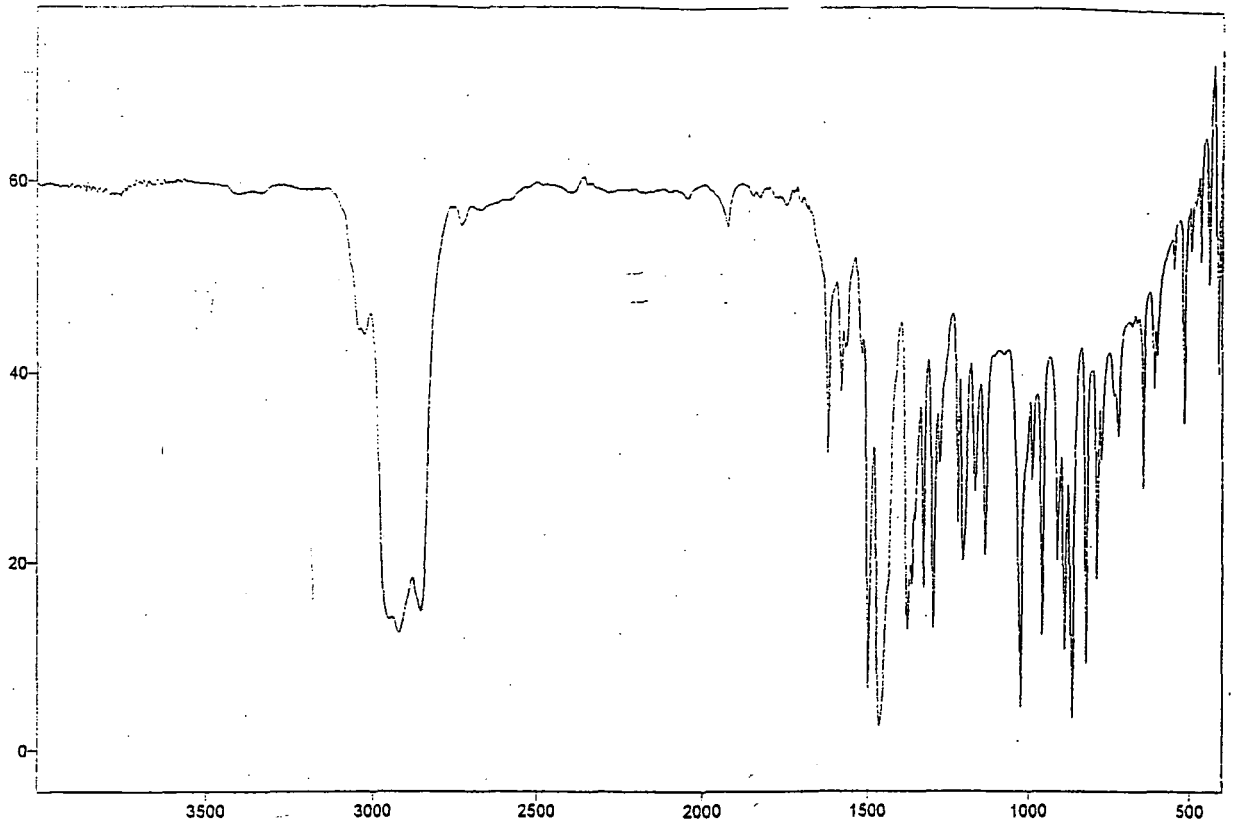
No. 31 6-Nitroquinoxaline (93)



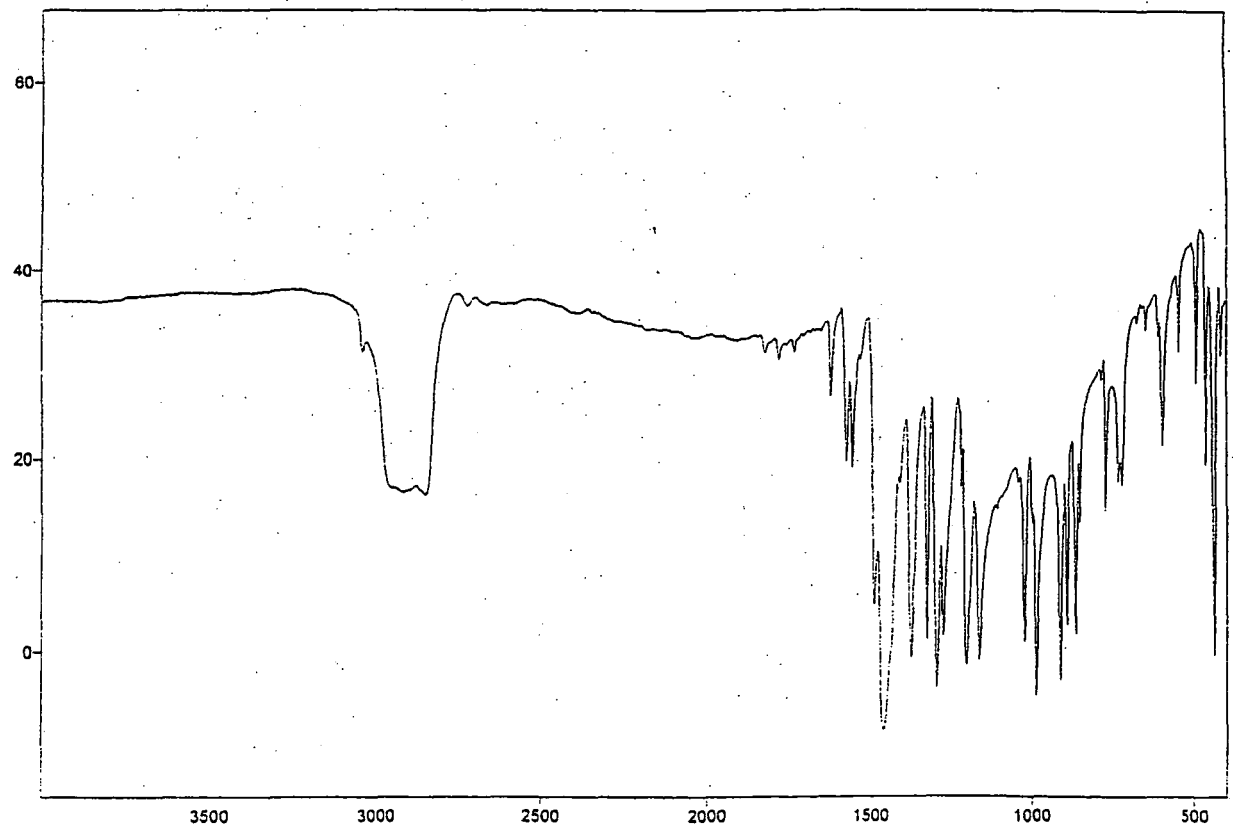
No. 32 2-Fluoroquinoxaline (95)



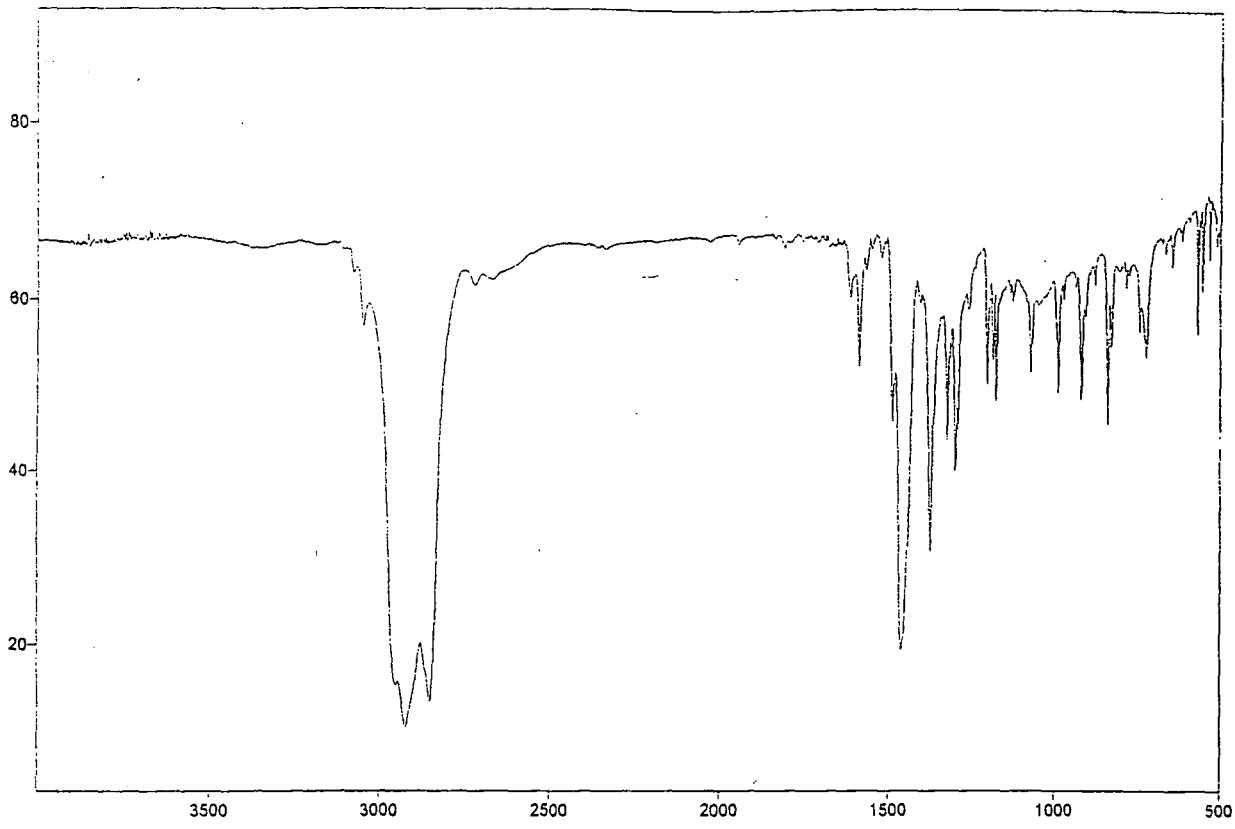
No. 33 2-Fluoro-6-methylquinoxaline (96A) and
2-Fluoro-7-methquinoxaline (96B)



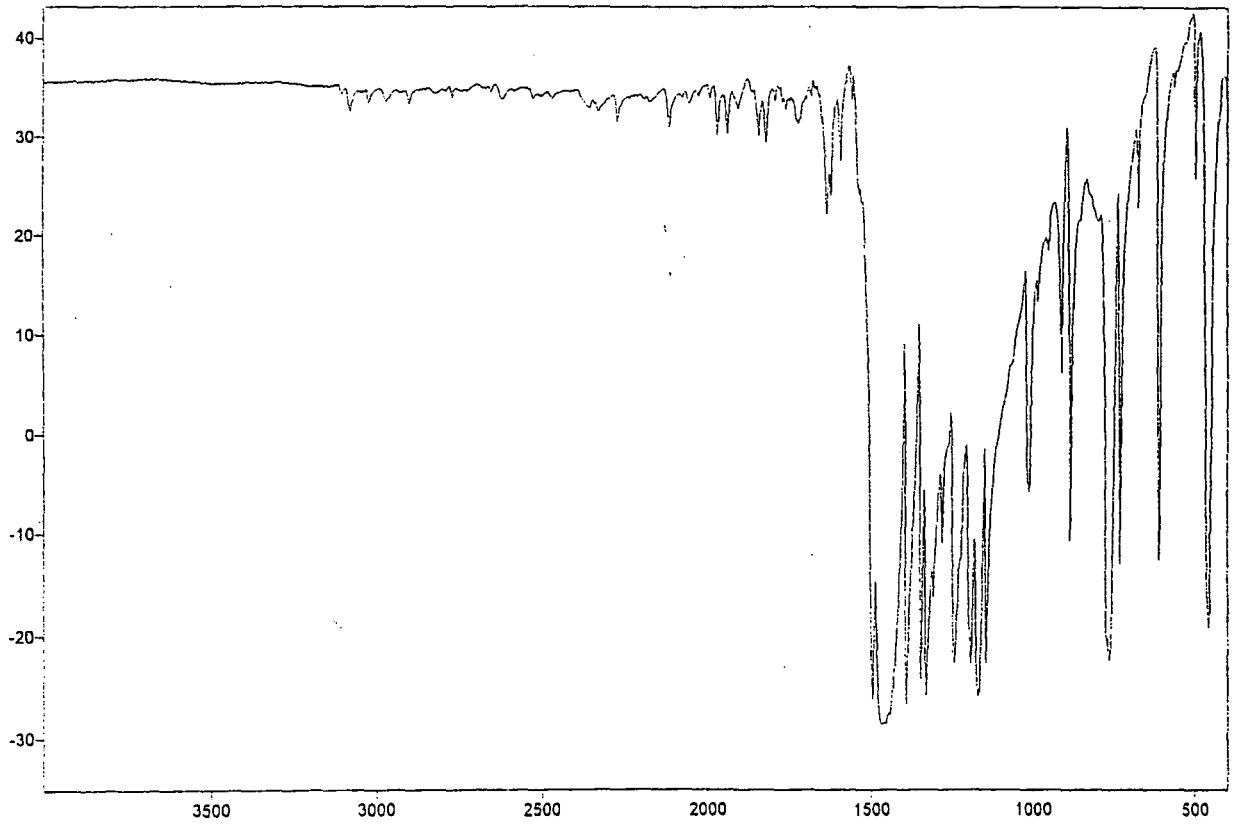
No. 34 2-Fluoro-6,7-dimethylquinoxaline (97)



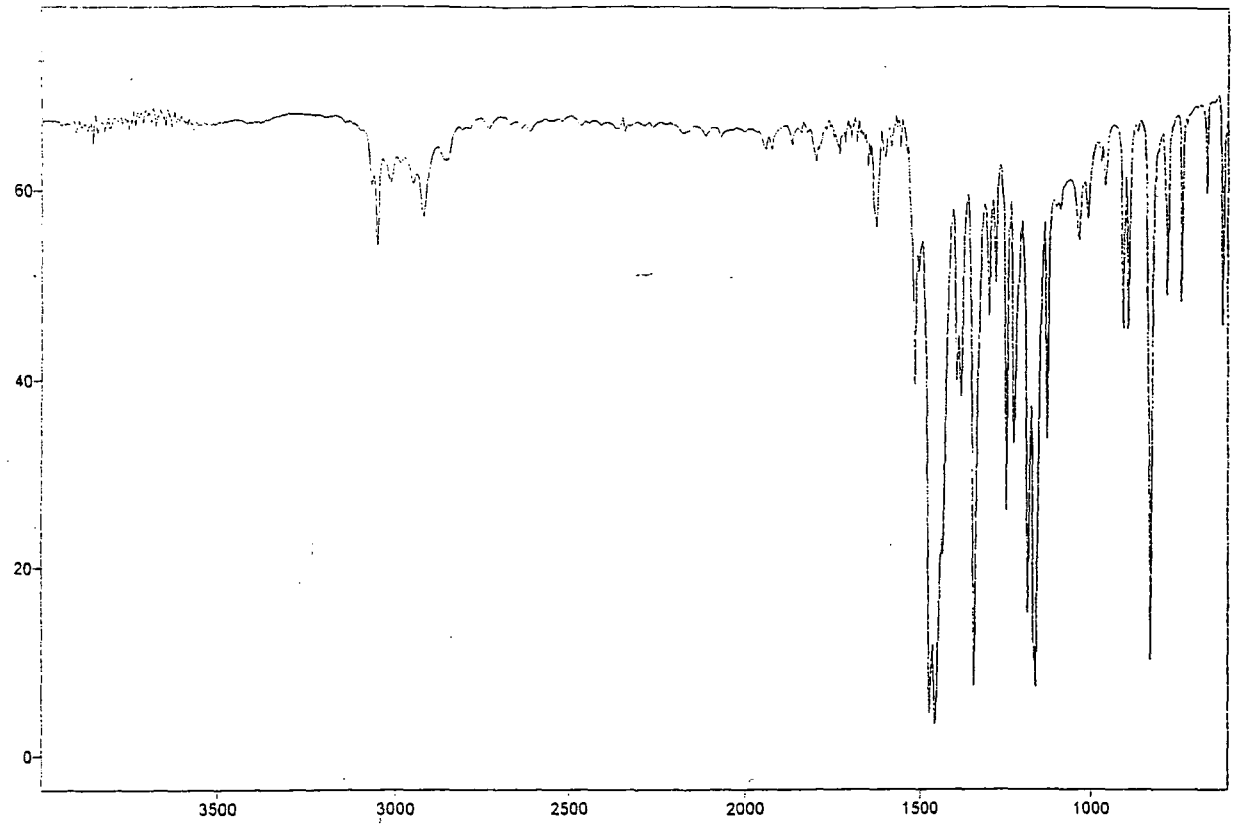
No. 35 6-Chloro-2-fluoroquinoxaline (98A) and
7-Chloro-2-fluoroquinoxaline (98B)



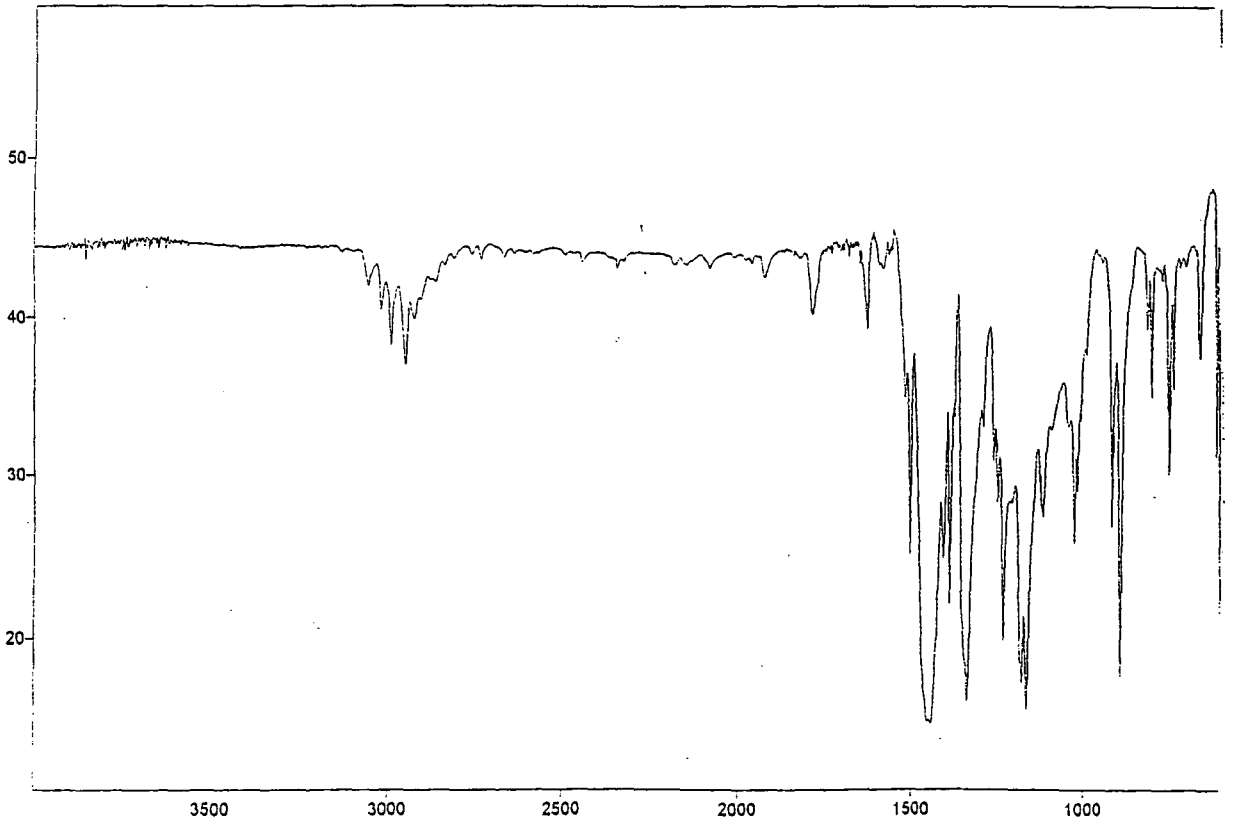
No. 36 2,3-Difluoroquinoxaline (100)



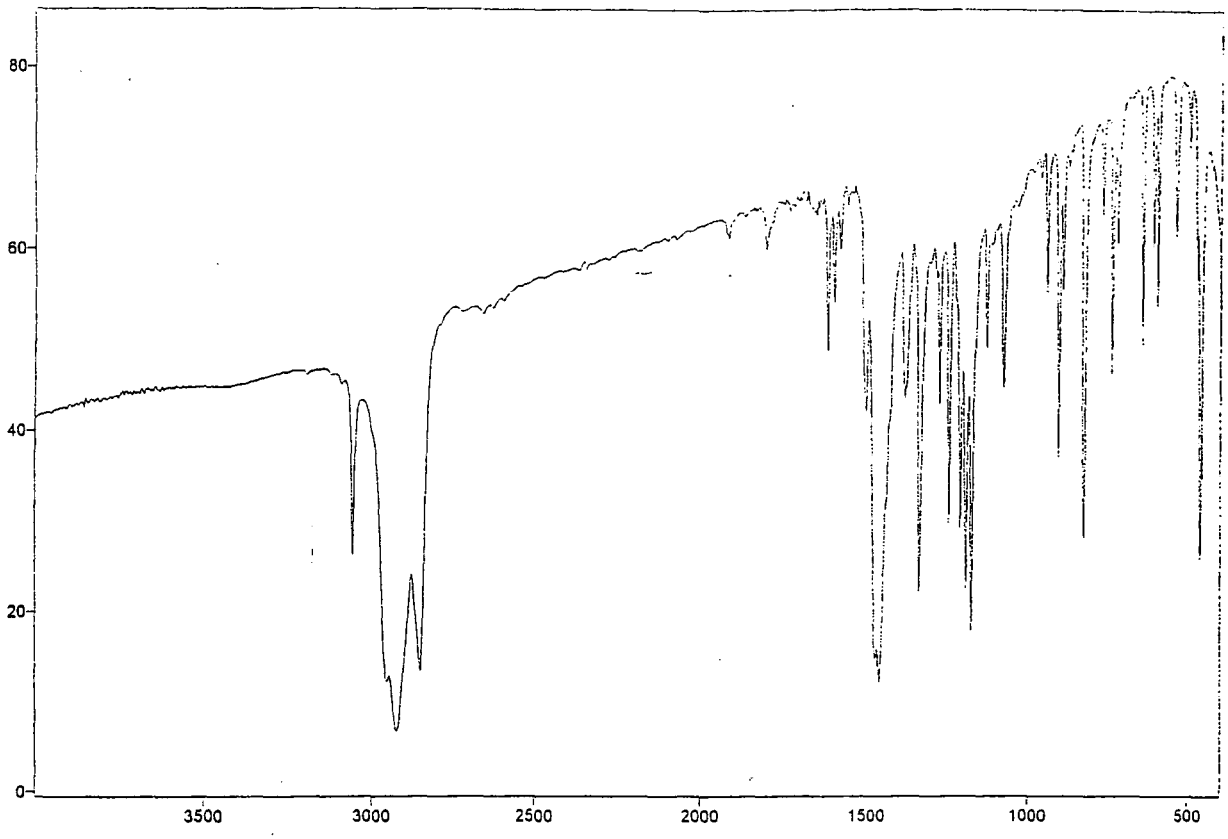
No. 37 2,3-Difluoro-6-methylquinoxaline (101)



No. 38 2,3-Difluoro-6,7-dimethylquinoxaline (102)



No. 39 2,3-Difluoro-6-chloroquinoxaline (103)



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